

TRANSCRIPT OF PROCEEDINGS
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL MEETING

VOLUME I

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July 21, 1998

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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL MEETING

Volume I

4898 86 86 JUL 29 AM 1:04

Tuesday, July 21, 1998

8:30 a.m.

Ballroom
Holiday Inn
Gaithersburg, Maryland

PARTICIPANTS

Tony W. Simmons, M.D., Acting Chairperson
John E. Stuhlmuller, M.D., Executive Secretary

MEMBER

Michael D. Crittenden, M.D.

CONSULTANTS APPOINTED TO TEMPORARY VOTING STATUS

Salim Aziz, M.D.
Jeffery A. Brinker, M.D.
Cynthia M. Tracy, M.D.
George W. Vetovec, M.D.

INDUSTRY REPRESENTATIVE

Gary Jarvis

FDA

Dr. Thomas Callahan

C O N T E N T S

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1 could affect their or their employer's financial interests.
2 Due to this prohibition, Dr. Anne Curtis will not
3 participate in today's session of this meeting. However,
4 the agency has determined that participation of certain
5 members and consultants, the need for whose services
6 outweighs the potential conflict of interest involved is in
7 the best interests of the government.

8 Waivers have been granted for Drs. Tony Simmons,
9 Jeffery Brinker, and George Vetovec for their interest in
10 firms that could potentially be affected by the panel's
11 decisions. The waivers granted for Drs. Brinker and
12 Vetovec allow them to participate fully in all matters
13 before the panel today. The waiver granted for Dr. Simmons
14 allows him to participate in all discussions, but not vote
15 on the PMA before the panel today.

16 Copies of these waivers may be obtained from the
17 agency's Freedom of Information Office, Room 12A-15 of the
18 Parklawn Building.

19 We would also like to note for the record that the
20 agency took into consideration other matters regarding Drs.
21 Brinker, Vetovec, Tracy, and Aziz. Each of these panelists
22 reported past occurring interest in firms at issue, but in
23 matters not related to the agenda for today's session.
24 Since their interests are unrelated to today's agenda, the
25 agency has determined that they may participate fully in all

1 discussions.

2 In the event that the discussions involve any
3 other products or firms not already on the agenda for which
4 an FDA participant has a financial interest, the participant
5 should excuse him or herself from such involvement and the
6 exclusion will be noted for the record.

7 With respect to all other participants, we ask in
8 the interest of fairness that all persons making statements
9 or presentations disclose any current or previous financial
10 involvement with any firm whose products they may wish to
11 comment upon.

12 Appointment to temporary voting status pursuant to
13 the authority granted under the Medical Devices Advisory
14 Committee charter dated October 27, 1990, as amended April
15 20, 1995, I appoint the following people as voting members
16 of the Circulatory System Devices Panel for this meeting on
17 July 21, 1998: Drs. Aziz, Brinker, Tracy, and Vetovec.

18 For the record, these people are special
19 government employees and are consultants to this panel under
20 the Medical Devices Advisory Committee. They have undergone
21 the customary conflict of interest review, and have reviewed
22 the materials to be considered at this meeting.

23 Signed, D. Bruce Burlington, M.D., Director of
24 Center for Devices and Radiological Health, dated 7-20-98.

25

Open Public Hearing

1 DR. SIMMONS: At this time, we would like to open
2 the meeting for the open public hearing. At this time,
3 nobody has asked for permission to speak, but is there
4 anybody that would like to speak?

5 [No response.]

6 DR. SIMMONS: In which case we are going to recess
7 the meeting until approximately 10:30.

8 [Recess taken from 8:50 a.m. to 10:50 a.m.]

9 DR. SIMMONS: I would like to call the panel
10 meeting back to session. We have already had the reading of
11 the conflict of interest and the open public hearing.

12 We are going to have the panel members introduce
13 themselves first. We will start over here. Dr. Callahan.

14 DR. CALLAHAN: I am Tom Callahan, Director of
15 Cardiovascular and Respiratory Neurology, FDA.

16 MR. JARVIS: Gary Jarvis, the industry
17 representative to the panel.

18 DR. VETROVEC: George Vetrovec, Medical College of
19 Virginia, Virginia Commonwealth University, Division of
20 Cardiology.

21 DR. AZIZ: Salim Aziz, University of Colorado,
22 Health Science Center, Denver, Colorado, cardiac surgeon.

23 DR. BRINKER: Jeff Brinker, Johns Hopkins
24 University.

25 DR. STUHLMULLER: John Stuhlmuller, Medical

1 Officer, FDA, Executive Secretary for the panel.

2 DR. SIMMONS: I am Tony Simmons, Wake Forest
3 University School of Medicine, Department of Cardiology.

4 DR. TRACY: Cynthia Tracy, Georgetown University.

5 DR. CRITTENDEN: Michael Crittenden, Harvard
6 University.

7 DR. SIMMONS: We will start with the company
8 presentation. This is Premarket Approval Application
9 P980003, Cardiac Pathways Corporation, Cooled Ablation
10 System.

11 **Company Presentation**

12 DR. ECHT: Good morning, ladies and gentlemen. My
13 name is Debra Echt, and I am the Chief Medical Officer and
14 Vice President for Clinical Research at Cardiac Pathways
15 Corporation.

16 [Slide.]

17 I will be presenting the results of the clinical
18 investigation of the Cooled Ablation System for
19 radiofrequency catheter ablation of ventricular tachycardia.

20 DR. STUHMULLER: Excuse me. For the record, we
21 need each of the speakers to get up and state what their
22 financial interest is.

23 It is up to you, if you want to get everybody to
24 just introduce themselves and what their financial interest
25 is now or do it as they get up to the podium, that is your

1 call.

2 DR. ECHT: I am an officer of the company.

3 DR. STUHMULLER: That is fine. You are an
4 employee.

5 DR. ECHT: Do you want to wait for the others?

6 DR. STUHMULLER: It is up to you, however you
7 want to do it, but what we just need to make sure is that
8 each person states their financial interest.

9 DR. SIMMONS: Why don't you do it as they come up.

10 DR. ECHT: Okay.

11 [Slide.]

12 The components of the Cooled Ablation System
13 consists of the radiofrequency generator, the ablation
14 catheter and associated tubing, and cables.

15 The Model 8004 radiofrequency generator
16 instrument, shown here, delivers a maximum power of 50
17 watts. The user interface is a touch screen and the
18 instrument is unique in that it incorporates an integrated
19 fluid pump.

20 [Slide.]

21 The cooled ablation catheter is a 7-French
22 deflectable quadripolar catheter with a 4 mm tip, and is
23 available in two curve sizes. The catheter contains two
24 lumens for flow into and from the tip. It is a closed
25 system, fluid is not delivered to the patient.

1 [Slide.]

2 Room temperature saline is infused through the
3 catheter to cool the catheter tip to minimize impedance
4 rises, and permit delivery of greater energy. Delivery of
5 greater energy results in larger and deeper lesion size,
6 which may be important to ablate ventricular tachycardia
7 circuits deep within the ventricular myocardium.

8 [Slide.]

9 Eighteen centers participated in the clinical
10 study of the Cooled Ablation System. They are listed here
11 in alphabetical order by principal investigator.

12 [Slide.]

13 A total of 188 patients were enrolled between June
14 30, 1995 and December 19, 1997. Patients were enrolled into
15 four study cohorts shown here, which will be described in
16 detail later in my presentation.

17 [Slide.]

18 The original study hypothesis was that people who
19 have received cooled radiofrequency ablation treatment of
20 ventricular tachycardia resulting from ischemic heart
21 disease will have a reduction in spontaneous and inducible
22 ventricular tachycardia when compared to patients treated
23 with antiarrhythmic drugs alone.

24 [Slide.]

25 The primary study endpoint was the clinical

1 recurrence of any ventricular tachycardia. The secondary
2 endpoints are inducibility of any mappable ventricular
3 tachycardia at the end of the ablation procedure, the
4 adverse event rate, and arrhythmic, cardiac, and total
5 mortality.

6 [Slide.]

7 The initial study design was randomized.
8 Randomization was 1 to 1 for the first 9 patients, and then
9 subsequently, 3 to 1 ablation to drug control.

10 Randomization was stratified by ventricular
11 tachycardia frequency, amiodarone use, and ejection
12 fraction.

13 Intention-to-treat analysis was also utilized.

14 [Slide.]

15 The randomized study entry criteria were as
16 follows:

17 Patients must have had two or more episodes of
18 sustained monomorphic ventricular tachycardia within the two
19 months prior to enrollment;

20 Ventricular tachycardia must have been due to
21 ischemic heart disease or non-ischemic cardiomyopathy. The
22 patients with bundle-branch-block reentry tachycardia were
23 excluded;

24 Patients must have had hemodynamically stable
25 ventricular tachycardia, but they could also have unstable

1 ventricular tachycardia;

2 Patients must have failed at least one
3 antiarrhythmic drug for the randomized study;

4 In addition, the first 9 patients enrolled in the
5 study were also required to have an ICD, and they must have
6 had ischemic heart disease, and they must have failed two
7 antiarrhythmic drugs.

8 [Slide.]

9 The randomized study protocol is shown on this
10 flow diagram. Eligible patients, after signing consent,
11 were randomized to either undergo an electrophysiology study
12 and cooled RF ablation of all mappable VTs at the same
13 setting, or an electrophysiology study followed by
14 optimization of drug therapy.

15 All patients were followed at one month, underwent
16 an electrophysiology study at two to three months, and then
17 were followed every three months for a year and at two
18 years.

19 [Slide.]

20 I will now present the results from the randomized
21 study. 107 patients were enrolled. 75 patients were
22 assigned to ablation, and 32 were assigned to control. The
23 demographic variables of the two groups were similar,
24 including age, ejection fraction, number of VT episodes in
25 the two months prior to enrollment, number of drugs

1 previously failed, and the number of VTs induced at the
2 electrophysiology study.

3 Of particular note is that patients had poor left
4 ventricular function with an overall ejection fraction of 30
5 percent. They had extremely frequent numbers of episodes of
6 ventricular tachycardias with an average of 20 episodes in
7 the two months prior to enrollment. They had previously
8 failed an average of 2 1/2 drugs per patient, and they had
9 almost an average of three different VT morphologies induced
10 at EP study, not just one.

11 [Slide.]

12 Most patients enrolled were male, which is
13 consistent with the prevalence of male gender in patients
14 with ischemic heart disease. Note that 40 percent of
15 patients had previously failed amiodarone. Almost three-
16 quarters had an ICD device, and overall, an average of 17
17 percent of patients had undergone previous VT ablation using
18 standard RF techniques, which had been unsuccessful.

19 Therefore, these patients represented a group with
20 advanced cardiac disease, who were refractory to drug
21 therapy, and had very frequent episodes of ventricular
22 tachycardia.

23 [Slide.]

24 The following definitions were used to assess
25 efficacy. Mappable VT was defined as VT that is sustained,

1 monomorphic, reproducible, and hemodynamically stable.
2 Acute success was defined as non-inducibility of any
3 mappable VT at the end of the procedure. Long-term success
4 was defined as no spontaneous recurrence of any VT at six
5 months.

6 [Slide.]

7 All patients underwent an electrophysiology study
8 prior to treatment. Ventricular tachycardia of some type
9 was inducible in 93 percent of patients assigned to
10 ablation, and 89 percent of patients assigned to control.

11 Because the study was analyzed by the intention-
12 to-treat, this meant that at least 7 percent of patients
13 assigned to ablation did not actually receive ablation and
14 therefore might be expected to have a VT recurrence.

15 To separate those VTs which were likely to be
16 hemodynamically stable from those which were not, a
17 conservative cutoff of 300 millisecond cycle length or 200
18 beats per minute was used to further categorize these VTs
19 that were induced. It is likely that VTs less than 200
20 beats per minute would be hemodynamically stable and
21 mappable, and therefore would be targeted for ablation.

22 Most patients had these slower VTs induced as
23 shown in the middle two bars, however, it is important to
24 note that 40 percent of patients assigned to ablation also
25 had fast VTs of less than or equal to 300 milliseconds, in

1 other words, faster than 200 beats per minute, which were
2 not likely to be mappable. So, a total of 47 percent of
3 patients, 40 percent with fast VTs and 7 percent
4 uninducible, might be anticipated to have a VT recurrence.

5 [Slide.]

6 The primary endpoint of the randomized study,
7 spontaneous recurrence of VT at six months, is shown in this
8 actuarial analysis. There were significantly fewer VT
9 recurrences in patients assigned to ablation, which is shown
10 in the solid line, compared to the drug controls shown in
11 the interrupted line, with a p equal to 0.0009 by the Gehan
12 test.

13 The six-month recurrence rate of 45 percent might
14 appear high at first glance, but again we believe this is
15 partly attributed to recurrence of VT not targeted by the
16 ablation procedure.

17 [Slide.]

18 The acute and long-term success is summarized on
19 this slide. The acute success rate determined at the end of
20 the ablation procedure was 75 percent. There was no
21 comparable measure of acute success for the control group.
22 The long-term success rate again was 55 percent for ablation
23 and only 19 percent for control, which was also
24 significantly different when analyzed here by the Fisher
25 Exact Test.

1 These results are similar to those in the
2 published literature. While it is difficult to directly
3 compare long-term success rates because most previous
4 studies did not use the same definition, acute success can
5 be compared.

6 [Slide.]

7 Results from eight published studies are
8 summarized on this slide. With a total of 190 patients
9 evaluated, the overall success rate was 67 percent, which
10 compares well to the finding in this study of 75 percent.

11 [Slide.]

12 This demonstration of efficacy in the randomized
13 study enabled a major study revision, eliminating
14 randomization and the requirement for prior drug failure.

15 [Slide.]

16 The non-randomized study protocol is depicted on
17 this flow diagram. Eligible patients, after signing
18 consent, underwent an electrophysiology study and cooled RF
19 ablation of all mappable VTs. Follow-up was at one month
20 with an EP study at two to three months and a final follow-
21 up visit at six months.

22 [Slide.]

23 For the assessment of safety, four patient cohorts
24 were pooled. The cohorts included patients in the
25 randomized study. They were assigned to ablation that we

1 just talked about. Seventeen of the 32 patients in the
2 randomized study assigned to ablation, but who had VT
3 recurrence, and crossed over to receive ablation, 18
4 patients treated under a compassionate use basis who met
5 study criteria, but had some contraindication to
6 randomization, and those patients enrolled after
7 randomization was discontinued.

8 A total of 173 patients were enrolled, but 150
9 were analyzed for the purposes of safety primarily because
10 the remainder did not have inducible or mappable VT, and
11 therefore did not undergo ablation.

12 We believe these four cohorts can be pooled
13 because the patient demographics, the acute and long-term
14 success, and the adverse event rate were all similar among
15 the four cohorts.

16 [Slide.]

17 The acute and long-term success rate shown here
18 for the randomized cohort, in yellow, and the pooled
19 patients, in blue, are quite similar, with again the acute
20 success rate being about 75 percent, and the long-term
21 success rate being 55 to 58 percent.

22 [Slide.]

23 The overall major adverse event rate in the pooled
24 patient cohort was 30 percent over the entire study duration
25 with a mean follow-up duration of eight months in a range of

1 two days to two years.

2 The individual adverse event rate for each cohort
3 is also shown with confidence intervals, further justifying
4 pooling. These overall adverse event rates include events
5 unrelated to the ablation.

6 [Slide.]

7 A Data and Safety Monitoring Board, composed of
8 independent experts, met regularly to monitor safety and
9 review events. This table lists the major and minor adverse
10 events that DSMB classified as potentially procedure
11 related.

12 The major adverse event rate was 8 percent with
13 four deaths, three non-fatal CVAs or TIAs, three cardiac
14 perforations, and two instances of third-degree heart block.

15 Nine minor adverse events, or 6 percent, were
16 classified as potentially procedure related, and are also
17 listed here.

18 [Slide.]

19 Overall survival in the pooled patients is shown
20 in this slide. The one-year actuarial survival rate was 80
21 percent.

22 [Slide.]

23 To put this data in perspective, the overall
24 survival is shown for the randomized study. This analysis
25 was performed in the most conservative way with control

1 I would like to thank all the members of the
2 review team for their hard work. Each member has provided
3 expert opinions in a timely and professional manner that
4 have aided in the expedited review of this application.

5 I would also like to thank the sponsor for
6 preparing a well-organized and complete PMA submission.

7 [Slide.]

8 Presently, there are three market-approved
9 ablation systems: EPT-1000 Cardiac Ablation System, which
10 was approved in October of 1994; the Medtronic CardioRhythm
11 Atakr Radio Frequency Catheter Ablation System, that was
12 approved in February of 1995; and the Cordis Webster
13 Diagnostic/Ablation Deflectable Tip Catheter, which was
14 approved in September of 1997.

15 I would like to point out that the Cordis Webster
16 Diagnostic/Ablation Deflectable Tip Catheter is approved for
17 use with a compatible RF generator. It is the Cordis
18 Webster Catheter, in conjunction with the compatible RF
19 generator, that makes up a cardiac ablation system.

20 [Slide.]

21 Market approved cardiac ablation systems have been
22 approved for: interruption of accessory atrioventricular
23 conduction pathways associated with tachycardia, the
24 treatment of AV nodal re-entrant tachycardia, and creation
25 of complete AV nodal block in patients with a difficult to

1 control ventricular response to an atrial arrhythmia.

2 [Slide.]

3 In contrast, the Chilli Cooled Ablation System is
4 indicated for cardiac EP mapping, delivering diagnostic
5 pacing stimuli, and for RF ablation of ventricular
6 tachycardias attributable to ischemic heart disease or
7 cardiomyopathy.

8 [Slide.]

9 The Chilli cooled ablation catheter is comparable
10 to market-approved ablation catheters. The diameter,
11 electrode length, and spacing of the Chilli catheter are
12 comparable to other market-approved ablation catheters. It
13 has two deflectable curve sizes, standard, enlarged, and a
14 temperature sensor is embedded in the tip electrode.

15 However, the tip electrode cooling feature of the
16 Chilli catheter is unique to it.

17 [Slide.]

18 I would like to take a moment to discuss the
19 closed lumen irrigation feature in a little more detail
20 because this is the topic of Question No. 10 in your handout
21 that you have been asked to address today.

22 This feature incorporates a closed lumen
23 irrigation system that cools the tip electrode of the
24 catheter. It is hypothesized that this feature will reduce
25 the amount of coagulum formed at the tip and allow RF energy

1 to be delivered for a longer duration than without cooling.
2 These hypotheses have not been studied.

3 In comparison, market approved ablation catheters
4 measure a temperature that is meant to be representative of
5 tissue temperature. This temperature may not be actual
6 tissue temperature, however, it has been shown to closely
7 approximate tissue temperature.

8 Since the Chilli catheter incorporates a saline
9 cooling feature to cool the tip electrode, and this is the
10 same location where the temperature sensor is embedded, the
11 recorded temperature may be much lower than that recorded
12 with market approved ablation catheters.

13 Additionally, it is not known if the recorded
14 temperature from the Chilli catheter is even proportional to
15 actual tissue temperature.

16 [Slide.]

17 The specifications for the cooled ablation
18 generator have been compared to specifications for market
19 approved RF generators. Initially, it is important to note
20 that the cooled ablation generator does not operate in
21 temperature-controlled mode, as other market approved
22 generators do.

23 It is also important to note that maximum cutoff
24 limits for the temperature, impedance, and duration
25 specifications are greater than those of market approved

1 generators. Please note that the following topic is
2 addressed in Question No. 9 of your handout. No clinical
3 studies have been performed with the cutoff limit set to 110
4 degrees C and 500 ohms.

5 FDA has identified a concern about the safety of
6 the proposed maximum cutoff limits. In response to our
7 concerns, the sponsor has proposed labeling which would
8 advise the operator to use maximum cutoff limits of 100
9 degrees Celsius and 200 ohms instead of modifying the
10 device. However, we believe it would be safer to have a
11 generator limited to maximum cutoff limits that were
12 evaluated in the clinical study.

13 [Slide.]

14 Pre-clinical testing has been conducted and
15 reviewed by the FDA's cooled ablation review team. At this
16 time, the sponsor is in the process of conducting additional
17 EMC testing and validating their sterilization process. We
18 do not expect that the outcome of these results will affect
19 the clinical data collected.

20 [Slide.]

21 In February of 1997, we sent a homework assignment
22 to a few of you on the panel at that time. You were asked
23 to provide comments on the safety and effectiveness of study
24 designs for ventricular tachycardia investigations.

25 Questions were asked about the appropriate control

1 group to use, how to determine the appropriate sample size,
2 and what endpoints should be used for measuring
3 effectiveness and how long the baseline period should be for
4 patients who act as their own control.

5 Your feedback was used to aid us in determining
6 which major protocol modifications were approved in May of
7 1997 when the randomization was discontinued in the cooled
8 ablation study.

9 [Slide.]

10 That table analyzes the observed adverse event
11 rate for all patients treated with the Cooled Ablation
12 System. There was a 30 percent observed major adverse event
13 rate among all patients who received ablation therapy with
14 the Cooled Ablation System, and an 8.7 minor adverse event
15 rate.

16 There were 26 deaths during the course of the
17 study, however, only 6 of the deaths occurred during the
18 initial hospitalization.

19 [Slide.]

20 In this table, the major adverse events have been
21 stratified by events which occurred acutely or were the
22 result of sequelae that occurred acutely, where acute has
23 been defined as one week post ablation.

24 There were 6 deaths, 3 CVAs, 3 cardiac
25 perforations, 1 electromechanical dissociation, and 2 third-

1 degree heart blocks.

2 [Slide.]

3 I have stratified the mortality data one step
4 further in order to provide supporting information for
5 Question No. 3 in your handout.

6 This slide provides the six-month mortality
7 results for both the control and the ablation patients who
8 participated in the randomized study. As you can see, there
9 was a 13.8 percent mortality rate for ablation patients,
10 where there was only a 6.3 percent mortality rate for the
11 control patients.

12 It is important to note that the crossover
13 patients have been censored.

14 [Slide.]

15 Acute and chronic effectiveness have been analyzed
16 for each patient cohort. The randomized to ablation was
17 70.8 percent acute success and 55.4 percent chronic success.

18 Control crossover patients had an 82.4 percent
19 acute success and a 70.6 percent chronic success.

20 Compassionate use patients observed a 70.8 percent
21 acute success and a 53.3 percent chronic success.

22 Non-randomized patients observed a 79.2 percent
23 acute success and a 51.2 percent chronic success.

24 I believe that it is appropriate to evaluate the
25 effectiveness of the Cooled Ablation System by only using

1 the randomized cohort, however, I think that it is
2 interesting to note how similar the chronic success for the
3 randomized cohort, the compassionate use, and the non-
4 randomized patient cohorts are. You can see there are 55.4
5 percent, 53.3 percent, and 51.2 percent.

6 [Slide.]

7 In conclusion, I would like to discuss the primary
8 and secondary endpoints which characterize the safety and
9 effectiveness of the Cooled Ablation System.

10 The primary endpoint was a decreased recurrence of
11 clinical VTs at six months. This endpoint has been met
12 since the Kaplan-Meier table entitled, "Randomized Study: VT
13 Recurrence at Six Months," which is attached in your handout
14 at the back, presents confidence intervals for ablation and
15 control groups which are statistically different at the six
16 month point.

17 [Slide.]

18 The two secondary endpoints I would like to
19 discuss are the major adverse event rate and the mortality
20 results of the randomized study.

21 The major adverse event rate associated with the
22 Cooled Ablation System is higher, 30 percent, than the
23 adverse event rate associated with medical management, 9
24 percent. However, it is comparable to the adverse event
25 rate reported in published studies for ventricular

1 tachycardia.

2 In addition, there may be a higher mortality rate
3 for patients who receive ablation as compared to patients
4 who receive drug therapy, 13.8 percent versus 6.3 percent
5 respectively. However, analysis of the data have not been
6 found to be statistically different.

7 DR. SIMMONS: The primary reviewer for the panel
8 is going to be Dr. Tracy.

9 DR. TRACY: Thank you. In reviewing this packet,
10 I came across several areas where I wanted to concentrate
11 some of my questions. We will start with very simple things
12 that are sort of technical issues, and then I would like to
13 go into some more detail about the different patient groups
14 because I had a bit of a problem figuring out exactly what
15 the flow of patients was, so I want to clarify that as we go
16 along here.

17 Just to start out with simple things, how was a
18 drug success defined, what was the definition of successful
19 drug intervention?

20 DR. ECHT: For the drug arm?

21 DR. TRACY: Yes, for the control arm.

22 DR. ECHT: That was done using individual
23 physicians, clinical personal definitions. There was not an
24 overall study definition.

25 DR. TRACY: So, it wasn't as defined by

1 electrophysiologic suppression of inducibility or holter
2 monitor, there wasn't a standard definition used?

3 DR. ECHT: There wasn't a standard. It was either
4 by EP testing or monitoring depending on the patient how
5 frequent their episodes of VT as how they decided whether
6 the antiarrhythmic drug was optimal.

7 DR. TRACY: We will come back to this, but I agree
8 with the FDA reviewer that device labeling, page 218, the
9 cooled tip ablation is referred to as a low risk procedure,
10 and I think that is something that we are going to have to
11 consider given that complications occurred in 44 out of 150
12 patients, but I think we will leave that until the end here.

13 I wanted to also understand the issue of how these
14 impedance limits were defined. 500 ohms is pretty high, and
15 why is the operator going to be expected to choose a high
16 and low impedance limit, and on what basis is that choice
17 going to be made by the individual operator?

18 DR. ECHT: It is not recommended that they go up
19 to 500 ohms. It is recommended that they go up to 200 ohms,
20 and that is the way we--

21 DR. TRACY: Is there a scientific basis for
22 choosing the impedance ranges, and how is the operator going
23 to know--as I understood the device, you have to set what
24 your high and low impedance limits are--how do you know
25 where to put the limits?

1 MR. RILEY: I am Rick Riley. I am the Vice
2 President of Research and Development at Cardiac Pathways.

3 Initially, when the RF generator was developed, we
4 were looking at competitive RF generator systems and what
5 they did with impedance and impedance limits. One of the
6 ones we looked at, at the time, was a radionics device that
7 was used. This was some five or six years ago.

8 At that time, that radionic generator had cutoffs
9 up to 500 ohms, and that is how we picked from the device
10 point of view, its upper limit.

11 When we got more experience with the device, we
12 set some lower and upper boundary conditions for the
13 operator to choose based on their experience with ablation
14 systems where they like to set the device. So, we left it
15 up to operators' experience to set the device, either at the
16 low end or the high end of the impedance.

17 Typically, generators don't need more than about
18 250 to 300 ohms in the high end, and usually nothing below
19 50 ohms on the low end just from the way ablation works.
20 So, when we went to the clinical study, and when we set the
21 parameters, sort of the default parameters in the device
22 itself, we picked 50, and I believe we picked 200 just for
23 those cutoffs and left those in the device.

24 So, we left some flexibility in the design at the
25 initial design of the device, and that is really the reason

1 for that. Then, we did set them in the clinical study
2 somewhere between 50 and 200 or 250.

3 DR. TRACY: To understand correctly, does the
4 device cut off if it doesn't deliver if you are below, and
5 it cuts off if you come above?

6 MR. RILEY: That is correct. If it goes below 50
7 ohms, it automatically shuts off, and if it goes above
8 whatever it is set--

9 DR. TRACY: Do you have any idea what the average
10 impedance was measured during the study, do you have that
11 data available?

12 DR. ECHT: What we have in the panel pack is the
13 maximum impedance, average maximum impedance, which was 160
14 plus or minus 70 ohms. We don't have the average impedance
15 data available today.

16 DR. TRACY: In the section on safety and
17 effectiveness, just a couple of brief statements on page 3-3
18 of that section. It talks about alternative therapies and
19 saying that drugs are not suitable for pregnant women
20 because of potential teratogenic effects.

21 I don't know what that is, but neither would be an
22 ablation during pregnancy, so I am not sure what that
23 statement is doing there, that a drug is teratogenic, but
24 what. It is more of a comment that I don't know how or why
25 that statement would be included there as an alternative

1 practices and procedures.

2 It is in the panel packet, Section 3, that is
3 entitled, "Summary of Safety and Effectiveness Data," and
4 it's page 3-3, Section 6, under Alternative Practices and
5 Procedures, in the second paragraph.

6 DR. ECHT: I agree with you. I didn't remember it
7 was actually in there. I agree.

8 DR. BRINKER: Some of the thinking about that may
9 be that if you do an ablation before the patient is
10 pregnant, it may obviate the need for drugs, and if you
11 chose not to do an ablation, but keep the patient on drug
12 therapy, then, the patient who may want to become pregnant
13 would be exposed to drugs.

14 The strategy of drug therapy versus ablation may
15 have some benefit, ablation versus drug therapy may have
16 some benefit in a patient who had child-bearing potential.

17 DR. TRACY: It is possible, but I don't think it
18 belongs in a section on data safety and effectiveness.
19 There is no information provided here that would suggest
20 that doing an ablation having anything relative to do to
21 pregnancy is either safe or effective, so I just think that
22 doesn't belong as a statement in this section.

23 The one thing that was missing that I suppose is a
24 little bit of a historic thing is that sort of the MADIT
25 criteria for entry were not incorporated here. I would have

1 thought maybe that was because the protocol was initiated
2 before that study came out, but just an interesting thing
3 that wasn't there.

4 I wanted to understand the significance of the
5 lack of a coagulum formation associated with an audible pop.
6 A lot of times with impedance rises with standard catheters,
7 if you remove the catheter, you won't see obvious coagulum
8 formation.

9 There is a suggestion here that the lack of
10 coagulum formation with an audible pop suggests something
11 different. What is it that is suggesting, is it suggesting
12 that you are getting a deeper tissue crater, is it
13 suggesting that there is more myocardial damage, is there
14 something different about it? That is also in that Section
15 3, on page 12, that there is some discussion about the pop.
16 What are we getting?

17 This was in the animal study.

18 On the next page, the statement popping occurred
19 at about the same frequency in conventional and cooled
20 ablation. As observed during in-vitro studies, popping was
21 associated with an audible pop, fallen catheter tip
22 temperatures, subsequent impedance rise, and above it, it
23 says that the catheter tip was lodging and ulceration
24 remaining within the endocardium.

25 MR. RILEY: I will try to address this. I think

1 what you are getting at in terms of some of the statements
2 here is that with cooled ablation with the tip of the
3 catheter having the fluid flow through it during the
4 ablation, the metal of the tip does not get as hot as the
5 metal tips for standard ablation.

6 You still get popping as you do in standard
7 ablation with cooled ablation, the difference being that
8 often sometimes with standard ablation we found even during
9 these studies that the catheter was lodged, sort of stuck to
10 the endocardium somewhat. You know, you get sort of a tight
11 fit there, and we postulated that perhaps that was due to a
12 formation of coagulum around the metal tip and adhering to
13 the surface of the tissue.

14 With cooled ablation, the coagulum doesn't form
15 easily around the metal tip, so it doesn't--when it comes
16 out, it doesn't stick to the metal tip, in fact, the
17 coagulum is probably not significant in all cases.

18 So, most of these observations during the animal
19 studies were just to note that with and without cooling, we
20 had a similar incidence of popping at high power settings.
21 So, in other words, the cooling mechanism itself still
22 allowed popping to occur in the animal studies as it would
23 with standard ablation and with cooled ablation, but the
24 coagulum formation was noticeably different on the tip of
25 the catheter during those animal studies.

1 DR. TRACY: I guess the thing that I was a little
2 concerned about is we often before temperature control we
3 might have impedance rise, and you might withdraw the
4 catheter for that, and you would not necessarily see
5 coagulum at the tip of the catheter.

6 I am assuming here that you were also not seeing
7 coagulum formation at the tip of the catheter, but in this
8 study, there was some incidence of CVA, so I am wondering
9 where this thing is or if the pop is indicative of tissue
10 damage going internally, something different.

11 MR. RILEY: I don't think we believe it is
12 something different. We believe it is something that is
13 similar to happens with standard ablation. Remember that in
14 this study, I believe we were using power mode delivery even
15 in the standard ablation. We weren't using a temperature
16 control mode as a comparison. We were doing standard power
17 mode comparisons.

18 One of the interesting observations I believe
19 during this study was that we were able to apply more power
20 for a longer period of time with cooled ablation than we
21 were with standard ablation partly due to the immediate
22 popping that occurred with standard ablation versus cooled
23 ablation.

24 DR. TRACY: I know that this goes back and it may
25 not--this is a historic question, and it may not be

1 answerable, but I believe one of the statements is that
2 there would be some type of a comparison between standard RF
3 and this chill tip ablation, and yet the entire study was
4 set up, not as a comparative study between standard and
5 chill tip ablation, and I am curious why that was not done.

6 I know that is a big question to be asking today,
7 but I need to understand it.

8 DR. ECHT: The study predated my joining the
9 company, but actually two of our investigators were involved
10 in discussions with the FDA four years ago, and maybe they
11 would like to address this.

12 DR. STEVENSON: I am Bill Stevenson from Brigham
13 and Women's Hospital. I was an investigator for the study
14 and, as such, I received research support for performing the
15 study.

16 At the time that the study was being designed,
17 there was not, and there still is not, a radiofrequency
18 ablation system that is approved for VT ablation, hence, we
19 were discouraged from designing this trial to compare
20 standard, what was then available RF, with this system, and
21 were encouraged to pursue a trial that compared the two
22 antiarrhythmic drug therapy.

23 DR. TRACY: Now we come to a point a few years
24 down the road where we are being provided, we have a body of
25 literature to compare with, with standard catheter ablation

1 versus ablation with a chill tip, now we have this more
2 limited population, and it is not apparent on the surface
3 that there is a significant difference between chill tip and
4 standard ablation catheters. At least at this point it is
5 not apparent to me that that is true.

6 DR. ECHT: Right, that has not been tested, so
7 that is unknown, and that is not a labeling request that we
8 have.

9 DR. TRACY: I want to go through some of the
10 patient numbers just to be sure I understand how patients
11 are included in different groups.

12 There were 75 patients who were randomized by
13 intention-to-treat, and I think in Section 4 of the FDA
14 summary, on page 17, I need to understand how many patients
15 of those 75 received chill tip ablation therapy.

16 It looks like there were 9 patients in whom
17 mappable VT could not be induced, and there were 2 patients
18 in whom there was a mappable VT, but a good site wasn't
19 identified.

20 DR. ECHT: Let me point you to where that was
21 summarized from the investigational study results that would
22 have been summarized. Page 6.3.2-6.

23 In that bottom paragraph, a total of 75 patients
24 did not actually receive ablation lesions in 9 patients
25 because mappable VT could not be induced prior to ablation,

1 and in 2 patients because mappable VTs were induced, but no
2 acceptable VT ablation targets were identified. That is
3 where those two numbers came from.

4 DR. TRACY: So, it is 75 minus 11, is that right,
5 64 patients?

6 DR. ECHT: Yes, and if you look on the next page,
7 for instance, we have also--

8 DR. TRACY: But there were an additional 5
9 patients who were not inducible?

10 DR. ECHT: And then there were 3 patients who
11 didn't receive lesions using the Cooled Ablation System, but
12 were ablated with commercially available catheters, and the
13 reasons for that are given, so that if you look at Table
14 6.3.2-5, you will see that the acute success is also shown
15 in the subset of patients who actually received cooled
16 ablation lesions.

17 Also, is shown, if you go into I think it's
18 Appendix 5 and 6, there is a flow diagram for Appendix 5 is
19 by intention-to-treat, and the flow diagram for Appendix 6
20 is only those 61 patients who had cooled ablation lesions,
21 and it shows the acute and chronic efficacy, Appendix 5 and
22 6.

23 DR. TRACY: I was having a lot of problems
24 following these people through. So, there were 61 patients
25 who got chill tip ablation?

1 DR. ECHT: In the randomized cohort of 75--

2 DR. TRACY: In the randomized cohort.

3 DR. ECHT: --who actually got ablated with cool
4 tip, right, because of the intention-to-treat and a few
5 other individual situations.

6 DR. TRACY: Sticking with those 61 patients,
7 during the follow-up time period on them, I understand a
8 decision was made to continue the patients on medications,
9 the same medications that they were at the time of their
10 ablation therapy, and the rationale being that was the only
11 thing that was desired to be the variable.

12 DR. ECHT: Exactly. They were kept on--asked to
13 be kept on ineffective therapies, so that that would not be
14 a variable.

15 DR. TRACY: You could make the argument that you
16 don't know what an antiarrhythmic will do in the setting of
17 a fresh lesion of unknown size and depth within a
18 ventricular myocardium. You don't know that that wouldn't
19 have introduced a possibility of proarrhythmia in a new
20 infarcted area of tissue, or you don't know that the--I mean
21 you just don't know what that antiarrhythmic meant.

22 DR. ECHT: Right.

23 DR. TRACY: So, I am not sure that that really
24 was--I don't know what else I would have done about it, but
25 I am not sure what it means to have done that.

1 If you want to look at the tables in the appendix
2 that you pointed me out to, 6.3.2-62?

3 DR. ECHT: Appendix 6.

4 DR. TRACY: Appendix 6?

5 DR. ECHT: Yes.

6 DR. TRACY: Acute effectiveness in 43 of the 61.

7 DR. ECHT: Yes.

8 DR. TRACY: Seventy percent. No recurrence of VT
9 at six months in 27.

10 DR. ECHT: Yes.

11 DR. TRACY: And that is 63 percent.

12 DR. ECHT: Yes.

13 DR. TRACY: Now, just to be sure, these 61
14 patients all received ablation therapy with the chill tip
15 catheter to a mappable lesion.

16 DR. ECHT: Yes.

17 DR. TRACY: And 43 were deemed to be effective, 27
18 had no recurrence at six months, and in the acutely
19 ineffective patients, there were 18, and of those, 7 had no
20 recurrence at six months?

21 DR. ECHT: Yes.

22 DR. TRACY: How does the 7 of 18 compare to the 27
23 of 43, is that statistically significantly different?

24 DR. ECHT: The 7 of 18 versus the?

25 DR. TRACY: The 27 of the 43, the 2 no

1 recurrences?

2 DR. ECHT: It was not statistically significant.
3 I believe that some of those relationships--okay, you are
4 looking at--tell me again, 11 over 18 versus 16--

5 DR. TRACY: You have two groups. You have
6 initially ablated them. Either it was acutely successful or
7 acutely unsuccessful. Then, the no recurrence rate in the
8 acutely successful was 63 percent, the no recurrence rate in
9 those that were ineffective was 39 percent.

10 I just wonder if those two groups are different.

11 DR. ECHT: If you look at the text on page 10,
12 which is Table 6.3.2.8., the relationship between acute and
13 long-term success is shown by intention-to-treat and cooled
14 ablation. It is not exactly--it is sort of related to what
15 you are asking. Whether or not long-term success was
16 predicted by acute success, and it wasn't, and I think that
17 if I had to try to understand it, it would be because the
18 long-term success indicator was such a sort of all-
19 encompassing, you know, any VT, and probably half of these
20 patients had non-targetable VT in addition to targetable VT,
21 that we were unable to show that having acute success led to
22 a long-term success because there are so many recurrences
23 that were probably attributed to non-targeted VTs. I think
24 that that is what that shows.

25 DR. TRACY: So, for any given individual patient,

1 the chance of the recurrence of the clinical VT is lessened,
2 but their overall chance of having a therapy delivered
3 because of VT, either related to defibrillator therapy or
4 something else, is high. Is that fair to say?

5 DR. ECHT: Right, and so, in fact, having the
6 control group, because the primary endpoint of the study was
7 so nonspecific, but the controls in the ablation patients
8 were treated similarly, the way that you see the benefit of
9 ablation is looking at the Kaplan-Meier actuarial analysis
10 for recurrence and showing the substantial difference
11 between the two groups.

12 DR. TRACY: So, in other words, it sort of factors
13 out all the non-targeted VTs that led to nonspecific--

14 DR. CALKINS: Could I say one comment? Hugh
15 Calkins from Hopkins. I was an investigator and got
16 research funding.

17 I think the striking thing about the study, and
18 actually I think the study was very interesting, because
19 there has been lots of little studies done for VT ablation,
20 but no big, carefully done prospective studies, and I think
21 one of the striking things was, was, you know, the
22 recurrences did happen or VT did occur after VT ablation,
23 and I think that was something we learned from the study,
24 which is an important finding and real, but the striking
25 thing is, is that doesn't reflect the benefit the patients

1 had. I mean if you look at the mean number of shocks
2 patients were getting pre- and post-ablation, there would be
3 patients that would go from 50 shocks in the first two
4 months prior to ablation to 1 shock three months later for a
5 fast, sort of non-ablatable VT, and that would be called a
6 failure according to this analysis, but I think doesn't
7 reflect a benefit, but I think it is true that patients are
8 not, at least the patients in the study, with the EF's of 30
9 percent, they don't live VT-free even if they had an acute
10 success as far as mappable VT.

11 DR. TRACY: I understand that, but I also see that
12 the mortality was three times as high in the ablation group
13 as in the control group, so I want to keep going to talk
14 about the control group.

15 DR. ECHT: I would love to address this issue that
16 the mortality was higher because I think that is not true,
17 but we can wait until you want to talk about it.

18 DR. TRACY: Yes. We do need to talk about that,
19 but to talk about the control group, there was a fairly
20 significant percentage of the patients--the control group,
21 it doesn't sound like there was a standard definition of
22 what a success is for medical therapy, and then a
23 significant number of the patients in the control group were
24 discharged with their medications having been discontinued
25 at the discretion of the investigator, and then a lot of

1 them crossed over after having a recurrence, crossed over to
2 be ablated.

3 So, by the time you get far enough out with the
4 control group, you have a fairly small number of patients
5 who get terribly far out, and then I think that the
6 recurrence data on those 14 patients, I think it was 14
7 patients who made it a fair distance out on antiarrhythmic
8 therapy, the recurrence rate was 43 percent of VT on the 14
9 patients who continued as the control group.

10 So, how was a decision made to stop the
11 antiarrhythmic therapy in the control group, how did that
12 happen?

13 DR. ECHT: I think it only happened in several
14 patients. Maybe the investigators want to address that, but
15 my understanding was in several patients, that the feeling
16 was that the antiarrhythmic drugs were proarrhythmic, and
17 that might have caused--

18 DR. TRACY: Maybe we could have somebody address
19 that, because the issue of proarrhythmia was never mentioned
20 in the panel anywhere.

21 DR. STEVENSON: I think that this was a difficult
22 patient group to study, patients that are having frequent
23 recurrences of ventricular tachycardia who are agreeable to
24 undergoing a new investigational procedure.

25 Often, they would arrive on more than one

1 antiarrhythmic drug or sometimes intravenous antiarrhythmic
2 drugs, as well, such that an intravenous drug may have been
3 withdrawn or there may have a sense that in the case of the
4 amiodarone, which has a very long half-life, that amiodarone
5 may have been contributing to more frequent slower episodes
6 rather than suppressing episodes. The drug may have been
7 discontinued recognizing that it would take some time for
8 the effect to dissipate.

9 I haven't specifically looked at that or seen that
10 data to know exactly how that went.

11 DR. TRACY: I think Section 4--again back to the
12 FDA summary page 18--kind of gives you a flow of the control
13 patients.

14 DR. ECHT: On Table 12 on page 12, it shows that
15 of the 32 control patients, 31 were taking antiarrhythmic
16 drugs at the time they were enrolled, and then 19 of 24, so
17 it looks like in the case of 4 patients out of the 32, that
18 drugs were stopped at hospital discharge, but then by the
19 time they are seen at two to three months, they were all on
20 drugs again. It goes back to all but 1. Actually, prior to
21 that they go back, that was apparently a short-lived--

22 DR. TRACY: At that point, by the time we get to
23 the two to three months, it looks like the 17 had crossed
24 over to the ablation group. So, it seems a bit of a setup
25 to fail drug therapy if the drugs are stopped, and then when

1 you have a recurrence, that you are ablated.

2 DR. ECHT: Four out of 32 had drugs stopped
3 because it was felt in those cases that the antiarrhythmic
4 drugs may have been contributing to a greater number of VT
5 episodes rather than fewer.

6 DR. TRACY: Where did the other 8 patients go
7 between enrollment and hospital discharge?

8 DR. ECHT: In those patients, the case report
9 forms were not completely filled out. They didn't go
10 anywhere. They were followed for a minimum of six months,
11 but the antiarrhythmic drug portion of that case report form
12 was incomplete.

13 DR. TRACY: I guess it still gets down to that
14 last group of patients, that last 14 that remained in the
15 "control group," and 6 of those 14, or 43 percent, were free
16 of recurring arrhythmias.

17 DR. CALKINS: Actually, between the four of us, we
18 had most of the patients that were in the study represented
19 here, and I know none of us, when we had a patient
20 randomized to a control, would say look, let's stop the
21 antiarrhythmics and see if--I actually don't call it optimal
22 drug therapy unless I thought it was proarrhythmic or had
23 some specific reason.

24 I don't think that the investigator, certainly I
25 didn't and I am sure these other three didn't say look, take

1 a randomized control, best drug therapy is no drug therapy,
2 let's stop it and see if they have VT.

3 You know, these patients, they were referred often
4 for ablation, and we had to put them on drugs, but we would
5 do our best to maximize it. A lot of them were on
6 amiodarone anyhow, there is not much more you can do when
7 you get to that point, so we would do the best we could
8 because of the study design, but I think this represented
9 sort of the reality this is the best we can do with drugs,
10 and there is only so many combinations and permutations you
11 can sort of add up together.

12 DR. TRACY: I think the reality is that somewhere
13 along the line, a lot of these patients, very many of them
14 crossed over at the time of some kind of clinical
15 recurrence, and I guess of those clinical recurrences, how
16 many of those patients were on antiarrhythmics at the time
17 of the recurrence, can we pin that down?

18 DR. ECHT: I bet I could have someone do that
19 really quickly if we look in the Excel file, demo union,
20 look at the control crossover. I probably don't have that
21 at the tip of my tongue. We will probably have to look that
22 up. We have all the sort of data files, and we can go back
23 and look that up, but it would take a while.

24 DR. TRACY: I don't know that that population of
25 those that crossed over necessarily should be pooled in with

1 the rest because it seems like whatever decisionmaking went
2 into wanting to do an ablation on those people--

3 DR. ECHT: Well, they were pooled only for safety,
4 not for efficacy, and, in fact, if you look at that sub-
5 cohort in terms of both demographics and acute long-term
6 efficacy and adverse event, they were similar, relatively
7 similar, so they probably are poolable for safety, we think.

8 DR. TRACY: I know other people are going to want
9 to jump in here pretty quick, so let me just try to hit a
10 couple more points very quickly.

11 If we could look at page 6.3.2-6, just to go
12 through, there were 30 patients who were assigned to
13 ablation who had VT of less than 300 milliseconds, which was
14 unmappable, it was too fast, and 5 patients were non-
15 inducible. The last statement in that paragraph, 35
16 patients, or 47 percent, were expected to have had
17 incomplete ablations. That is because they were left with
18 fast VTs that were not addressed?

19 DR. ECHT: Those are not absolute numbers. We did
20 not use actually the criteria of 300 milliseconds, so some
21 VTs that were faster than 200 beats per minute may have been
22 ablated, and some that were slower may have been
23 hemodynamically unstable, and not have. We used that as
24 sort of a cutoff to try to just kind of get an idea of how
25 many of these patients were likely to have.

1 We did not actually require them to stipulate how
2 many were not targeted.

3 DR. TRACY: A couple questions about specific
4 patients. There is a statement made somewhere in there
5 about there were no deviations made on inclusion/exclusion
6 criteria, but there was a patient in there who had what the
7 patient himself considered to be terminal cancer and
8 declined further therapy, and there was also a patient who
9 went on the next day to CABG and aneurysmectomy.

10 How did those two patients get into the protocol?

11 DR. CALKINS: The patient with terminal cancer was
12 ours, and he had sort of a slow prostate CA, where his life
13 survival was actually supposed to be relatively long, but
14 because he has had the name of cancer, whatever, he declined
15 the defibrillator for that reason, but he wasn't lung CA
16 about to die in two months, he was sort of five, 10-year
17 whatever survival.

18 DR. TRACY: So, it was a slower malignancy. Okay.

19 DR. ECHT: The real advantage to having the
20 investigators with the highest volumes here.

21 DR. STEVENSON: The CABG patient, it was
22 anticipated that he may need revascularization, but after
23 his first VT ablation failed and he continued to do poorly,
24 that was felt to be another option to try and bail him out.

25 DR. TRACY: How many patients required two

1 ablations at sort of the first setting?

2 DR. ECHT: After the pooled or for the randomized,
3 for the randomized sub-cohort or the pooled?

4 DR. TRACY: Either way.

5 DR. ECHT: I will show you. That is on procedural
6 safety data, page 16. Of the 75 patients randomized to
7 ablation, there were 74 procedures, 54 had 1, 10 had repeat,
8 and 11 didn't get ablated, so there were 10 that had
9 repeats.

10 DR. TRACY: I guess just the final point I would
11 like to talk about is the mortality data.

12 DR. ECHT: Okay.

13 DR. TRACY: What accounts for the late mortality
14 in the ablation group? One of the figures that you showed
15 this morning, there is like a late drop-off at about Day 500
16 or 400.

17 DR. ECHT: All the deaths are described in the
18 appendix, and they are, for the most part, end stage heart
19 failure.

20 DR. TRACY: End stage heart failure?

21 DR. ECHT: But I would like to say that it is
22 inappropriate to look at crude mortality rates when the
23 follow-up durations were so markedly different between the
24 ablation and the control patients as we have analyzed them
25 here.

1 The median follow-up for the ablation group was
2 one year. The median follow-up for the control group was
3 less than three months. So, to look at total mortality,
4 which were again mostly, you know, later, you can't, and
5 that is why we showed the Kaplan-Meier curve, which takes
6 follow-up duration into consideration.

7 If you wanted to look at crude mortality rates,
8 actually, there are two other ways to do it that was
9 actually recommended to be actually more relevant by the FDA
10 statistician.

11 One way you could look at it is just take those
12 control patients who did not ever cross over, so subtract
13 the 17 that crossed over, and if you looked at their crude
14 mortality, 16 percent was like the same as in the ablation
15 group.

16 The internal statistician here felt that that was
17 probably the best way, and if you really wanted to do it
18 correctly by intention-to-treat, where the crossover
19 patients are still considered in the determination of
20 mortality, in fact, there is 22 percent, so, in fact, you
21 know, there is a trend toward more deaths in the controls,
22 but I don't think that is fair, but that is by purist
23 intention-to-treat.

24 So, I don't think that there is any reason to
25 believe that there are any significant differences in total

1 mortality between the two groups.

2 DR. TRACY: In the long term, the group comparing
3 the controls who stayed as controls, that mortality I would
4 expect would be the same, it was just hard to get to a point
5 where you could see that.

6 DR. ECHT: Yes.

7 DR. TRACY: And the acute complications or the
8 major adverse events are there.

9 DR. ECHT: Right, there is no question, but if you
10 would sort of just look at total--I mean if the question is
11 survival, there was no difference between the groups.

12 DR. TRACY: I think I will stop. I have other
13 questions, but I know other people have other perspectives,
14 so I will be quiet.

15 DR. SIMMONS: Do you want to start, Dr.
16 Crittenden?

17 DR. CRITTENDEN: I would like, if I could, to
18 listen to other comments.

19 DR. SIMMONS: Okay. Dr. Aziz.

20 DR. AZIZ: I just have a few technical questions
21 from a pharmaceutical point of view.

22 If you had a patient who was having recurrent VT
23 in an acute post-myocardial infarct situation, I assume
24 these other patients have mitral regurge, I guess using this
25 procedure with the intra-aortic balloon would be a

1 contraindication, would that be right?

2 DR. ECHT: Since I am not a doctor anymore, I am
3 going to ask the investigators if they want to comment on
4 that.

5 DR. STEVENSON: The use of catheter ablation with
6 an intra-aortic balloon, we have actually not in this
7 protocol, but we have actually done that on one occasion,
8 and did not encounter any problem with passing the catheter
9 beyond the balloon in the aorta. Inflation of the balloon
10 against the catheter did introduce an artifact which was
11 apparent in the electrical recordings.

12 This combination of devices wasn't specifically
13 addressed in this trial, and I am unaware of any patients
14 being treated with an intra-aortic balloon to try and
15 support them during mapping.

16 DR. ECHT: There has been one patient, I think
17 very recently, subsequent to this PMA submission, who did
18 undergo the procedure with an intra-aortic balloon.

19 DR. AZIZ: Particularly in a patient with low EFs
20 and mitral regurge, it might give you a window of sort of
21 safety, because it seems like those are the ones that do
22 give you problems. It looks like you have already done
23 patients who had previous mediastinotomies and things of
24 that nature without any--

25 DR. STEVENSON: Yes.

1 DR. AZIZ: There was one patient I think who died,
2 who I think when he did get a perforation, you couldn't do
3 pericardiocentesis because of the patch being present.

4 DR. CALKINS: There was one patient that we had,
5 that had a perforation, that we couldn't tap acutely because
6 of the patch being in place, and the patient went to surgery
7 and had surgical repair, had a small hole in the outflow
8 tract, and that was surgically repaired.

9 So, that was the one that I am aware of as far as
10 a patient who died from perforation. I remember that
11 description, but that was a case that he had a patch, so we
12 couldn't enter the anterior pericardial sac percutaneously,
13 so he ended up getting a surgical repair.

14 DR. AZIZ: Usually, when you have adhesions, it is
15 difficult to get tamponade.

16 DR. CALKINS: It was ulcerative posterior. The
17 patient eventually recovered and went home.

18 DR. AZIZ: In the patients who did die, was
19 histology done of the heart at all, was that looked at, at
20 the site where the ablation was performed? I didn't see any
21 histology.

22 DR. ECHT: We did have histology performed on the
23 patient who died with a CVA. This patient had a mural
24 thrombus, and it is likely, but the pathologist wasn't able
25 to absolutely say, but it is likely it actually predated the

1 ablation from the dating of it.

2 There is no question that it caused the CVA and
3 that the same dated material was found in the middle
4 cerebral artery. The patient ultimately herniated a week
5 later that caused the death.

6 DR. AZIZ: Those are the questions I had.

7 DR. BRINKER: I just have a few. One of the
8 problems with the deliberation of this kind of therapy is
9 that we are looking at two problems. One is the
10 justification, at least from a non-electrophysiologist line,
11 for ablation for ventricular tachycardia, since there is no
12 acceptable predicate.

13 The second is the device itself, if it is any
14 unique apparatus.

15 The one question I have is, is it clear amongst
16 the electrophysiologic community that VT ablation, if this
17 device wasn't approved, that the off-label use of device,
18 that it is a standard of care for stable VT, which is what
19 this is basically aimed at?

20 DR. WILBER: I would like to take the opportunity
21 to address that. My name is Dave Wilber from the University
22 of Chicago. I am an investigator, but otherwise have not
23 received any other compensation.

24 The issue as far as whether VT ablation is
25 considered a standard part of practice, actually, it was, as

1 you know, one of the first arrhythmias that catheter
2 ablation was applied to.

3 The latest NASPE registry that collected data,
4 which I think was in 1994, there were something like 1,000
5 ablation procedures or 1,500 ablation procedures done for
6 ventricular tachycardia. Unfortunately, we don't have
7 current estimates now of how wide the off-label use is, but
8 we have some idea that it is potentially in the range of
9 perhaps as many as 1,000 per year in the United States.
10 That is not just for ischemic heart disease, though. That
11 includes all VT ablations.

12 Once again, I can't speak for the VT community,
13 but I certainly think that the data would suggest that it is
14 a very common procedure. There is actually data on safety
15 and risk for VT ablation that have gone back a long time.
16 The NASPE registry, which again, unfortunately, was most
17 recently published in 1994, and also the multi-center
18 European registry looked at the risks of VT ablation, for
19 example, and, in fact, the mortality rate for VT ablation,
20 and unfortunately pooled data, so they weren't looking at
21 this particularly high-risk patient, but all that were done,
22 and, in fact, the mortality rate was about 2 percent in both
23 of those registries.

24 It deals with a sick population. Now, if you look
25 at the population of patients that were done in this

1 particular study, it is very comparable to the kinds of
2 patients that undergo surgical ablation, whereas, as you are
3 aware, the mortality rate in the best of centers is in the
4 range of 5 to 10 percent over the first 30 days.

5 So, I think these are the realities of the numbers
6 that we are dealing with. These are sick patients. When
7 these patients have been taken for surgical ablation, in
8 fact, a much higher mortality was accepted as being
9 reasonable given the kind of disease that they had and the
10 frequent recurrences they had had.

11 I would submit we enrolled about--I think the
12 largest number of patients in the series--and I would submit
13 that all of the patients that we enrolled are patients that
14 we would have either considered for surgical ablation or, in
15 fact, were too sick and would not have been considered for
16 surgical ablation because we didn't think they would have
17 survived the surgery.

18 So, I think that at a minimum, the population was
19 comparable to the kinds of people we take to VT surgery, so
20 I think what we are really talking about comparing, we are
21 talking about catheter ablation and procedures for catheter
22 ablation for VT are the standard surgical mortality, which
23 is 5 to 10 percent, or the published mortality that is in
24 the literature, that is somewhere around 2 or 3 percent for
25 the acute procedural mortality for VT ablation.

1 DR. BRINKER: Let me ask you a couple more
2 questions. You can educate me a bit more about this.

3 The VT, when you ablate it, basically, has to be
4 mappable.

5 DR. WILBER: That's right.

6 DR. BRINKER: As your conservative definition of
7 mapping, it is probably a true one that the heart rate has
8 to be below 200 per minute.

9 DR. WILBER: You know, it obviously varies on
10 hemodynamics and ejection fraction. I think it is a fair
11 estimate. In our experience in patients, in our total
12 experience, which is now about 70 patients for VT ablation
13 with ischemic heart disease, similar to this protocol, I
14 would say it is somewhere in the range of 40 to 50 percent
15 have very rapid VTs that we can't match, so the surrogate
16 endpoint that was used here, which was VTs greater than 200
17 beats per minute, I think is a reasonable guesstimate of
18 what was mappable and what isn't.

19 Now, unfortunately, that varies from place to
20 place and what you are willing to do. Our general
21 operational definition is a systolic blood pressure of 80
22 and that the patient doesn't have other symptoms. So,
23 obviously, rate may vary a little bit, but once again, I
24 think the general idea that about 40 percent of patients
25 that come to ablation are going to have unstable VTs that

1 can't be targeted by our current mapping techniques is a
2 very reasonable one. In fact, if you look in the
3 literature, I think it is fairly constant at that number.

4 DR. BRINKER: So, these more stable VTs, do you in
5 your heart of hearts think you are changing the life
6 expectancy of the patient?

7 DR. WILBER: I would expect that we are not. I
8 don't think that is the issue for these patients.

9 DR. BRINKER: That is an important point.

10 DR. WILBER: I don't think that the suggestion
11 here is that VT ablation necessarily makes people live
12 longer, although I think in a subgroup of patients, we could
13 argue that. These patients, the ones that came to these
14 protocol, it was done for quality of life or palliation of
15 their VT, given a therapy that for most of these patients,
16 given the number of drugs that they failed, continue to face
17 recurrent episodes of tachycardia.

18 You are talking about patients who had an average
19 of 20 episodes of VT or more in the two months prior to
20 their procedure, so these are patients that were getting--75
21 percent had defibrillators, they were getting multiple
22 shocks. I can tell you that the quality of life for the
23 people that came to this study was quite poor actually.

24 So, the question is, if the purpose I think in
25 this particular case is to palliate the disease, and there

1 are patients where it may be curative, I don't know that
2 there is sufficient data in this study to address it. I
3 think that will be the basis of future studies, but I think
4 the claim for this study is not that survival is prolonged.
5 I don't think it is shortened, and I think that the other
6 comment that hasn't been made about survival in this study
7 is that patients who have recurrences tend to be the
8 sickest.

9 So, in fact, when you take those patients out of
10 the control group, what you are doing is taking the sick
11 people out, so that to say that the mortality of whoever is
12 left, and look at that, doesn't make a lot of sense.

13 So, in other words, you really can't compare the
14 mortality the way it has been done. It makes no sense. You
15 have taken the sickest people out because as soon as they
16 have their recurrence, they are taken out, they get an
17 ablation, but yet those people face the risk of mortality
18 down the road.

19 My argument was that the best way to look at
20 mortality for this particular device would have been an
21 intention-to-treat, and simply look at mortality in both
22 groups on an intention-to-treat basis, just as efficacy was,
23 and if you do that, there is clearly no difference in
24 survival.

25 DR. BRINKER: I think that is an important point.

1 Did the patient have to have only one form of VT, one site
2 of VT?

3 DR. WILBER: No.

4 DR. BRINKER: How vigorous was multiple sites or
5 pathways looked for?

6 DR. WILBER: Actually, the idea of the protocol
7 was to ablate as many stable VTs as you could. The
8 investigator was allowed the option of how many is that,
9 well, once again, it was not uncommon for an individual
10 patient to have two or three stable morphologies.

11 I think that when it gets in the range of five or
12 six, the investigator certainly had the option that it was
13 perhaps prudent to stop, but, in fact, in general, our
14 policy has been to try to ablate as many stable VTs as
15 possible.

16 DR. BRINKER: These procedures I think averaged
17 around four hours or so with almost an hour of fluoroscopy
18 time, and one of the questions that the FDA will pose to
19 you, I think is how much special training or preparation
20 does one need to perform these procedures.

21 As an operator, do you think that there is a
22 specific training requirement for an electrophysiologist who
23 is otherwise doing RF ablation, perhaps not VT ablation, but
24 as you suggest, there is so much off-label use of RF or VT,
25 maybe there is, but is there a need for special training of

1 a credentialed EP person in this technique?

2 DR. WILBER: It is a difficult question to answer.
3 I think that, frankly, there is a need for special
4 credentialing for people to do ablation, period. As to
5 whether or not beyond being an electrophysiologist, but I
6 think that is a broader issue for another time.

7 DR. BRINKER: Let's say VT as opposed to ESVT.

8 DR. WILBER: As opposed to an accessory pathway.
9 I think this gets to issues about accreditation and
10 involving ACGME.

11 DR. BRINKER: I don't mean that. I mean should
12 the company require some sort of training session or
13 something like that.

14 DR. WILBER: I think that perhaps something in the
15 same sort of thing that was done for--if the availability of
16 this device will suddenly increase the number of VT
17 ablations that were done, or to have centers do them that
18 would not have otherwise done them, then, that probably
19 would be prudent.

20 I guess my question is I am not sure that the
21 approval or not of this device will suddenly increase the
22 number of VT ablations being done. I think there is a fair
23 number of those being done by a variety of catheters at the
24 present time.

25 I do think that as with any new technology--this

1 would be the first approved technology for VT ablation--I
2 think that it would be prudent to continue both some kind of
3 training, once again in a limited sort or fashion. I don't
4 that anyone, once again, in terms of specific ablation
5 skills, one can have a course to do that, and teach somebody
6 in a weekend how to ablate VT if they haven't been taught
7 that before.

8 DR. BRINKER: Just one last thing. I think for
9 the labeling, I mean it should be clear, I think, that this
10 is in most patients not a definitive procedure to eliminate
11 VT. It is unlikely that most patients will be taken off
12 drugs I believe from your data, is that correct? Most of
13 the patients were still on some antiarrhythmic drugs.

14 DR. ECHT: Part of that was protocol required. I
15 think we could ask the physicians what they would do if they
16 weren't in the study.

17 DR. BRINKER: Well, I don't think you can do that.
18 I think what you can do is just put the experience that this
19 study showed, and maybe that's the best thing is to say that
20 of X number of people that received ablation, Y number
21 remained on drugs and Z number had recurrences, and there
22 was A, B, and C experiential deaths, major events, and minor
23 events.

24 I wasn't initially impressed with Cindy's comment
25 about pregnant women being saved anything by this, but as I

1 look at that whole section now where it gives the benefits
2 and disadvantages of ICDs and surgery, et cetera, I think
3 that this may not be an alternative--it is not an
4 alternative to an ICD, and it is not an alternative to drug
5 therapy, so I think that one has to give the idea that this
6 may be a right step in palliation for most patients, but not
7 a cure for most patients.

8 DR. WILBER: I appreciate having the opportunity
9 to comment on that. I think we have to be very cautious
10 about what we say VT ablation can and can't do based on the
11 present data that we have.

12 I certainly think for a large part of the
13 population, it is palliative. My only concern is that there
14 are patients in probably subgroups that you can't analyze by
15 looking at this data, although others have looked at it,
16 that, for example, patients that have good ventricular
17 function, for example, in isolated inferior infarct, and a
18 single morphology VT, that, in fact, we have several of
19 those patients that have gone home and done well, and have
20 no alternative therapy.

21 I think it would be perhaps incautious to tell
22 people that it is only palliative. I think that in some
23 patients, it is not just palliative, it is curative. I like
24 your idea of saying these are the facts, this is the
25 population they are in, these are the facts, these are the

1 results.

2 I am just not sure, it might be incautious to make
3 more sweeping statements based on the present data because
4 we haven't analyzed all the subgroups yet, and I think if
5 you look at that or if you request that data, it may be
6 provided, but I think there are subgroups that may benefit.

7 DR. BRINKER: Well, once that data is available
8 and is found to be validated, then, appropriate labeling
9 changes can be made, and presumably the operators, whoever
10 does these ablations, will have some insight as to who they
11 think is the optimal candidate, but I think to extrapolate
12 on anecdotal kinds of findings, the labeling becomes a big
13 issue. I think the more conservative we are with that, the
14 better off everybody is going to be at this stage of the
15 game.

16 DR. WILBER: As an individual physician, as
17 someone who manages patients and does these sorts of
18 procedures, I have a concern about the implication of some
19 of these statements that, in fact, an ICD is the standard of
20 care for some of these patients, when I am not sure that
21 that is true.

22 Once again, when we come back to the patient with
23 an isolated inferior infarct that has an ejection fraction
24 of 40 percent and has recurrent episodes of VT that require
25 multiple hospitalizations, he is not at high risk of dying,

1 he is not part of the AVID trial, he wasn't included in
2 that, and once again, I think that if you make labeling
3 requirements that you would be cautious in the statement
4 that you don't imply that this--when you say it's an
5 alternative to ICD therapy, it implies that ICD therapy is
6 the right thing for all of these patients, and once again, I
7 think for patients with stable VT, particularly those with
8 good ventricular function, we don't know that that is true.

9 So, once again, I would just advise or ask the
10 panel that when they consider labeling indications, that
11 they keep all of these things in mind. I am not sure we
12 have a standard of care. There certainly have been drug
13 therapy for these patients, it has been the most common
14 thing we have done. We know that the recurrence rate on
15 drug therapy from any number of trials is in the 60 to 70
16 percent range over five years.

17 DR. ECHT: ICDs were not required, and more than a
18 quarter of the patients did not have ICDs, and there was not
19 excess morbidity in those patients.

20 DR. BRINKER: I am not suggesting that ICDs should
21 be implanted. I am just saying that in your section, the
22 way it reads now, as alternative practices, there is mention
23 of ICDs. You did that, not me, and all I am saying is that
24 what should be said is just the facts of this study and that
25 X number of patients were on ICDs, X number of patients

1 needed to have drugs.

2 Just one other comment. Was there an incidence of
3 patients who did not have accelerated ventricular
4 tachycardia clinically prior to ventricular ablation,
5 develop accelerated ventricular tachycardias over the
6 ensuing follow-up period of time?

7 DR. ECHT: What do you mean by accelerated, more
8 frequent episodes?

9 DR. BRINKER: No, more rapid.

10 DR. ECHT: More rapid.

11 DR. BRINKER: Unstable ventricular tachycardias.

12 DR. ECHT: Forty percent had unstable tachycardias
13 before, and that makes it very difficult to know when
14 someone has it later. We don't know.

15 DR. BRINKER: On an individual basis, did anybody
16 have a patient that developed--

17 DR. WILBER: We have looked at this, and we have
18 had patients, although we at the end of our study, after the
19 ablation procedure and before, we actually tried to do a
20 very thorough study prior to the ablation procedure to
21 address just the issue that we had, because very early on in
22 our experience, we did occasionally see patients, not
23 necessarily with the cool tip, but in patients who had ICDs
24 with other catheters, and what we did see is occasionally
25 that for the first time after a procedure, a patient would

1 have a fast VT a year later.

2 In our experience, those were almost always
3 predicted by the induction of a rapid VT prior to the
4 ablation procedure. My own interpretation of this data, and
5 I think you can certainly talk to the other investigators
6 that are here, because I think this is currently a source of
7 scientific discussion amongst us, whether or not this
8 phenomenon we are seeing, rapid VTs afterwards, for the
9 first time after the ablation procedure is the disease
10 itself or something else.

11 Now, we know that, for example, there are
12 published series of patients who had only stable VT, there
13 is a certain incidence of sudden death over time, so clearly
14 we know in the absence of an intervention, there is a
15 certain small number of patients who have something more
16 rapid that is ultimately fatal when you follow them up over
17 time.

18 In our own experience, looking at the pre-ablation
19 induction of rapid VT as a predictor of post-ablation rapid
20 VT spontaneously, we only saw rapid VTs spontaneously in
21 those patients who had it at a previous time.

22 I am not sure, some of the other investigators may
23 have a little bit of difference, but we have been interested
24 in the same problem, so I don't know that we have an
25 absolute answer, but my impression has been from our data,

1 both with this catheter and others, that, in fact, the rapid
2 VTs are part and parcel of the disease that the patient has.

3 DR. BRINKER: Thanks.

4 DR. SIMMONS: I would like to make some comments
5 here because I don't agree with everything that was said
6 just right here, but it is time for a 10-minute break and it
7 is not my turn.

8 We are going to take a 10-minute break and then we
9 will come back.

10 [Recess.]

11 DR. SIMMONS: Our next reviewer is going to be Dr.
12 Vetrovec.

13 DR. VETROVEC: I will be fairly brief, but I have
14 a couple of questions and comments.

15 I would like for you, if you could, put up your
16 pooled patient cohort data. Can you just walk through with
17 me on this slide which patients were not analyzed and why?

18 DR. ECHT: Okay. Can you get back to that slide.

19 DR. VETROVEC: I couldn't follow it relative to
20 what was in the actual packet.

21 DR. ECHT: On page 17 of the text, the last
22 paragraph, it goes into detail.

23 [Slide.]

24 We were asked from the standpoint of safety to use
25 the definition--the definition that was used was whether or

1 not a cold catheter was inserted into the heart.

2 This, for the most part, includes sort of
3 virtually all of these patients were ablated with the cooled
4 ablation catheter, but I think there were one or two--and it
5 sort of goes into detail on this paragraph--who actually had
6 the ablation catheter inserted, it was probably used for VT
7 induction, but then they couldn't find a target and actually
8 deliver lesions, one or two, but for the most part, 75
9 patients were randomized to ablation, and these represented
10 patients who had inducible, mappable VT, and had the cooled
11 ablation catheter used or at least inserted.

12 These 17 patients were from the 32-patient control
13 group who then crossed over. These 18 patients were treated
14 in a compassionate use protocol where they had to meet the
15 inclusion criteria. This was during the randomized part of
16 the study. But they had some reason they couldn't be
17 randomized.

18 For instance, they had no other drug alternatives,
19 that was sort of a common, they had incessant VT and the
20 investigator felt that it wasn't reasonable to randomize
21 them to control.

22 Then, these last 63 patients were enrolled. What
23 we did is we used a very, you know, strict definition.
24 Enrolled means you signed a consent form. But then
25 ultimately, some of these patients, when they went to the EP

1 lab, they didn't have inducible, mappable VT, and so they
2 didn't get ablated with the cooled catheter, and that is why
3 these numbers are lower than these numbers.

4 DR. VETROVEC: Tell me something else, a little
5 bit about the complications. I don't do EP work, but the
6 complications seem relatively high to me of a serious
7 nature.

8 In a population which, although you bill it as
9 being quite ill, if in your pooled data you leave in the
10 procedure-related mortality, there is about only a 10
11 percent total mortality rate over one-year follow-up, so it
12 is not quite as devastating of a heart failure population as
13 predicted by other heart failure data.

14 So, on the one hand, yes, it is a very sick
15 population because it is having VT, but its mortality
16 doesn't look too bad over one year at least. So, it is kind
17 of a funny population, it seems to me, so I think the
18 complications somehow become very relevant to me, and I
19 guess more from the standpoint it is many different things,
20 but do you have some specific recommendations that you are
21 going to make in terms of is it better to do it across the
22 aortic valve only, is it better to do it transseptally, are
23 there some recommendations that you can make that might make
24 sense with that with the catheters?

25 DR. ECHT: One of the things we found in the study

1 is that anticoagulation is really critical, and that heparin
2 administration would probably be best monitored using ACT
3 levels, because there are some patients in whom large
4 heparin doses does not result in adequate anticoagulation,
5 and we have seen problems.

6 In fact, there was one revision to the study
7 protocol where ACTs had been recommended, but not required,
8 that they became required after one complication where the
9 patient received substantial doses of heparin, but was not
10 anticoagulated by ACT.

11 I think that is one thing that would be
12 recommended. I believe it is recommended in the labeling.
13 We could even be more strong about that.

14 The other common complications are perforations.
15 I would really like the investigators to comment on that. I
16 think that the incidence of cardiac perforations, even with
17 diagnostic EP, is probably substantially higher than we
18 think. I would be sort of interested in what people would
19 like to say that are practicing at this time.

20 DR. CALKINS: Hugh Calkins from Hopkins again.

21 Just a couple of questions about the complication
22 rate. Although 8 percent major complication rate, 8 percent
23 minor complication rate strikes anyone as high, I think when
24 we look at prospective studies that have been done with
25 catheter ablation for approved indications for SVT, the

1 CardioRhythm trial, for example, the major complication rate
2 there was 3 percent and the minor complication was 8
3 percent, and that was in a much healthier population that
4 has non-life-threatening, non-serious arrhythmias, so I
5 think if the complication rate is a little over twice as
6 high in a group with a mean EF of 30 percent versus a group
7 with a mean EF of 50 percent, and the age difference, or
8 whatever, I think it is sort of somewhat reasonable. Some
9 of the complications in the study, certainly the one that
10 made the protocol change because of the anticoagulation
11 issue, clearly could have been--not clearly--but almost for
12 sure would have been avoided with careful attention to
13 anticoagulation, so those likely would not recur.

14 We had one perforation which I think was more--I
15 don't think it was related to the cooled RF catheter per se,
16 but more to the underlying disease substrate, which was RV
17 dysplasia, which notoriously has a very thin outflow tract,
18 and that is where the perforation occurred, and I think that
19 could have occurred with any type of catheter, and more was
20 an inherent increased risk just given the substrate the
21 patient had, the arrhythmia.

22 DR. ECHT: The cardiac perforations are discussed
23 in the back, but they are sort of a variety of potential
24 etiologies, one related to a transseptal, one related to a
25 catheter in a tributary of the coronary sinus, and it is

1 hard to think of any, sort of one thing that we could
2 advise.

3 DR. VETROVEC: That was what was sort of
4 bothersome because you couldn't figure out--maybe this is
5 the nature of the beast, and maybe that is what EP ablations
6 are all about, I maybe don't have a feel for it, but it just
7 seems high to me.

8 I am a little concerned because you can't even
9 figure out except for the ACT--how about TEEs, is that at
10 all recommended because of the atrial thrombi?

11 DR. ECHT: That is an interesting issue, as well,
12 because the one thromboembolic stroke in a patient who
13 probably had a mural thrombus, a surface echo, it showed an
14 aneurysm, but did not define a mural thrombus within it.
15 Again, I would like to ask--I know that there are some
16 people who don't believe that transesophageal echoes are
17 substantially better at detecting mural thrombi, but I don't
18 know if anyone here wants to comment on that.

19 DR. STEVENSON: I think that we very frequently,
20 on transthoracic echoes have a report come back as "cannot
21 exclude thrombus," and our policy has been to not defer
22 ablation in those patients. We have not had any embolic
23 events in those people with attention to adequate
24 anticoagulation.

25 One of the exclusion criteria was a pedunculated,

1 what we view as a mobile thrombus, and I think that is an
2 important exclusion criteria for mapping the ventricle.

3 In terms of transesophageal echo to look for
4 atrial thrombi, that in my mind is really an issue only if
5 the transseptal puncture procedure is performed to access
6 the left ventricle via that route.

7 DR. ECHT: I can mention in that one particular
8 case of the lethal CVA, pathologically had a mural thrombus
9 and an aneurysm, that in that particular patient, the
10 patient had not been previously maintained on coumadin
11 therapy, but this patient had a barrage of VT episodes, and
12 the physician felt that he would rather risk doing the RF
13 ablation than what would likely be the outcome for the
14 patient if he required that the patient have three weeks of
15 coumadization prior to an RF ablation. It becomes a
16 difficult judgment issue.

17 DR. VETROVEC: An entirely different line of
18 questioning. Since this procedure is going on without
19 labeling in the environment, how many of the patients in
20 this study were done with this device because they failed
21 other non-label techniques?

22 DR. ECHT: Seventeen percent of the patients had
23 previous RF ablation using standard techniques that was
24 unsuccessful.

25 DR. SIMMONS: Dr. Crittenden, do you want to chip

1 in?

2 DR. CRITTENDEN: Really, I don't want to prolong
3 the discussion because I think everything that was important
4 was well said, and I think I would, if anything, thank Dr.
5 Brinker for bringing out a discussion that I needed, being a
6 surgeon, trying to understand all this. So, I appreciated
7 that discussion.

8 Just the one question I would have of one of the
9 investigators, I think the gentleman from the University of
10 Chicago addressed, but I would like to hear one other. How
11 would this fit in the algorithm of treatment for VT, in
12 other words, what do you think the role is for this, just
13 another adjunct? Is this the best treatment of three
14 treatments that are not good drug therapy and AICDs? Just
15 help me with the role for this.

16 DR. STEVENSON: As has been alluded to several
17 times, people that have monomorphic ventricular tachycardia
18 in the setting of structural heart disease often have
19 frequent recurrences of tachycardia, and that drug therapy
20 has not been particular effective in suppressing
21 recurrences. In fact, 50 to 70 percent of patients will
22 have a recurrent episode during long-term follow-up.

23 So, this therapy I think has great potential for
24 reducing the frequency of recurrent ventricular tachycardia
25 during follow-up, and, in fact, in our current practice,

1 what is tending to happen now is that the major source of
2 referrals for VT ablation are people with implantable
3 defibrillators where the device is having to terminate
4 symptomatic episodes relatively frequently.

5 I think from a practice standpoint, that is the
6 way I see this moving. I would agree with the comments that
7 Dave Wilber made earlier that there is a subset of people
8 who walk into the emergency room with VT at 140 beats per
9 minute, who don't have a defibrillator, who often have a
10 relatively smallish area of scar, where their arrhythmia
11 behaves, from the patient's standpoint, almost more like
12 it's a supraventricular tachycardia and where ablation is
13 very attractive for that group of patients, so that I, like
14 Dave, am a little concerned that if the labeling mandates
15 that this is an alternative for patients who have
16 defibrillators only, you may be excluding a group of
17 patients who would otherwise stand to receive quite dramatic
18 benefit.

19 DR. SIMMONS: Mr. Jarvis, do you want to comment?

20 MR. JARVIS: I have no comments.

21 DR. SIMMONS: I guess I have a few. I was
22 actually going to quote you, the fact is I will. There is
23 an article here in our panel pack by somebody named
24 Stevenson, that says, "The ease and efficacy of VT ablation
25 may be potentially enhanced by neuromapping ablation

1 technologies that are now entering clinical trials. Further
2 investigation is required to determine whether ablation
3 should become the major adjunctive therapy to the ICD safety
4 net." This is a 1998 article.

5 This seems to be, you know, the way I would have
6 viewed it, but this is not some of the opinions that have
7 been expressed here today, and yet this company has come
8 back to the FDA and asked for permission to not use the ICD
9 safety net, which I consider the definitive therapy for
10 patients with VT.

11 I don't believe in monomorphic stable VT that you
12 can go out there and have, and not die from--I mean
13 Medtronic died trying to make that anti-tachycardia
14 pacemaker work without defibrillator backup. I mean you can
15 have 100 episodes of stable monomorphic VT, and the 101st
16 one will kill you.

17 So, I would disagree with Dr. Wilber, if he wants
18 to do the study to prove that that patient with the inferior
19 wall myocardial infarction in one VT is safe from the
20 ablation, that is fine, but your own data would say he can't
21 do that. Your own data says that the pre-discharge EP study
22 doesn't predict who is going to be a chronic success.

23 So, I guess I am having trouble reconciling the
24 viewpoints here.

25 DR. STEVENSON: I certainly agree that we need

1 more data on this. The number of patients that have
2 tolerated VT, particularly not on an antiarrhythmic drug, is
3 very, very small, and there is just simply not good long-
4 term data.

5 We all have our anecdotal series. We have a
6 little series of 12 patients who hadn't previously failed
7 antiarrhythmic drug therapy, who have really done quite
8 well.

9 I will stand by what I said in that editorial. I
10 really do feel that ablation is going to be a major advance
11 in controlling frequent VT episodes in people with
12 defibrillators, and the defibrillator is a wonderful safety
13 net. I will stand by that, but I still think that there are
14 a small number of patients that stand to benefit who do not
15 presently have implantable defibrillators.

16 DR. SIMMONS: I think that is great. Certainly, I
17 take care of patients, too, and there are certainly people
18 that I would like to have that opportunity to do so, but
19 from a marketing standpoint, I mean we are not talking about
20 you and I, we are talking about the company marketing this
21 device, I would have to say in the absence of an ICD, it
22 should be some part of a clinical trial. That would be my
23 own bias is that if you are not doing some clinical trial,
24 the patient should have an ICD safety net.

25 I mean that is why I am disagreeing with what you

1 were saying here before. The ICD is the definitive therapy.
2 There is a standard of care for patients with concurrent
3 sustained monomorphic VT, and that is the ICD with a 97
4 percent success rate. This is an adjunctive therapy to
5 that, great, but outside those bounds, it is an
6 investigational study, and you need to do it.

7 Would somebody like to comment on that?

8 DR. ECHT: The ICD was only required in the first
9 nine patients, so more than a quarter of the patients did
10 not get ICDs.

11 DR. SIMMONS: That doesn't justify it.

12 DR. ECHT: That is a small number, but to say that
13 it hasn't been tested, you know, it wasn't required.

14 DR. SIMMONS: I think compared to the thousands of
15 patients in the ICD trials, this is--

16 DR. CALKINS: I think the interesting thing is the
17 question that someone with a VT rate of 110 beats a minute,
18 EF 50 percent--

19 DR. SIMMONS: On drugs, of course.

20 DR. CALKINS: No, off drugs, who walks into the
21 emergency room.

22 DR. SIMMONS: That doesn't happen.

23 DR. STUHLMULLER: I am sorry, can I interrupt
24 here. The purpose of the panel meeting today is to discuss
25 whether the device is safe and effective relative to its

1 proposed indications for use. I think we need to stay
2 focused on the issue, is this device safe and effective for
3 what the company has proposed as its indications for use.

4 DR. CALKINS: Just to answer the question briefly,
5 there are other places, they are rare, but--

6 DR. STUHLMULLER: I am sorry. We need to stay
7 focused on the issue, is the device safe and effective for
8 its proposed indications for use, and that is what we need
9 to stay focused on here today. There is a separate section
10 on future concerns in which we can address the issue of
11 clinical trial designs after the PMA discussion.

12 DR. SIMMONS: I sort of got off the track, too,
13 sorry about that.

14 Let me just go on. Do you have any evidence in
15 patients, in humans, that these lesions are deeper, wider,
16 anything at all, any evidence at all that the device creates
17 a deeper lesion with or without the cooling in humans?

18 DR. ECHT: Thankfully, very little. We have a lot
19 of animal--

20 DR. SIMMONS: There should be some on autopsy
21 data, shouldn't there? I mean a lot of patients have died,
22 don't you have cross-sections of lesions?

23 DR. ECHT: Bill? No, luckily, we have a
24 transplant heart that we have looked at.

25 DR. STEVENSON: We have histologic observations

1 from 18 days after ablation in a patient who had
2 compassionate use of the cooled catheter, and maximal lesion
3 depth occurred in one of the septal lesions was 7 mm. It
4 has a shape very similar to what we would anticipate from
5 cooling, kind of a rounded shape with a little bit narrower
6 neck at the endocardial surface.

7 The other lesions that were made by several
8 applications, so it wasn't possible to say what the size of
9 a single RF lesion was, but the lesions appeared consistent
10 histologically with what had been observed previously for
11 non-cooled RF with the one being a maximal depth, as I
12 mentioned, of 7 mm.

13 DR. SIMMONS: Which isn't that out of bounds for
14 what could have been accomplished with a non-cooled
15 catheter.

16 DR. STEVENSON: We don't have any direct
17 comparative data, and we do have histologic examination of a
18 heart from a non-cooled RF catheter where the lesions
19 appeared on the endocardial surface quite similar, but there
20 was no comparison of depth because that was a very thin
21 infarct region.

22 DR. WHARTON: Marcus Wharton from Duke University,
23 investigator for the trial.

24 DR. STUHMULLER: What is your financial interest?

25 DR. WHARTON: No other financial.

1 DR. STUHLMULLER: Have you received any
2 compensation from the company?

3 DR. WHARTON: Just for doing the investigation.

4 We did some studies in the canine model comparing
5 directly dose response curves for chilled ablation versus
6 standard ablation using the same catheter but not infusing
7 it with saline. At 20 watts, there was absolutely no
8 difference in width or depth or lesion volume between
9 traditional or cooled ablation, but at 30, 40, and 50 watts,
10 increasing width and depth, particularly depth, and thus a
11 significant increase likewise in lesion volume.

12 Importantly, this gets back to a question that was
13 asked earlier, if you look at the actual lesions up to 50
14 watts, no increased risk and no difference in the degree of
15 complexity, so no cratering at less than or equal to 50
16 watts, which I think is an important safety issue within the
17 power ranges that are being proposed for the use of the
18 catheter in the clinical, so there is good canine data that
19 there is a demarcation beyond 20 watts.

20 DR. SIMMONS: Is your data the data that is
21 presented in this PMA?

22 DR. WHARTON: I think it is in the animal data.

23 DR. SIMMONS: Because the way it is presented in
24 the PMA, is that at 30 and 50 watts, there is an increased
25 depth, but at 40 paradoxically, it was the same or less.

1 So, in the animal data, 30 and 50 watts created
2 deeper lesions, but 40 watts didn't, and this was explained
3 in the text as a statistical aberration based upon low
4 numbers. But couldn't this also be a bimodal type curve,
5 you know, with certain power settings, the heat of the tip
6 versus the current density energy are counterbalanced in
7 certain animal weights?

8 You could easily envision some sort of bimodal
9 distribution for depth versus width, for temperature versus
10 current density, that one might actually minimize the damage
11 as opposed to actually maximizing. I certainly can envision
12 a bimodal type distribution.

13 DR. WHARTON: I am not sure I understand. I
14 probably have the manuscript with me if you want to see the
15 data directly.

16 DR. SIMMONS: But I think we have to go with what
17 is on the PMA, and the PMA says at 40, it actually got less,
18 consistently less, not randomly less, but consistently less.

19 DR. WHARTON: If you look at the curves, it may
20 not have been statistically--

21 DR. STUHLMULLER: A point of procedure. If the
22 article is part of the PMA submission, then, you can discuss
23 the data that is in the article. If it is not, then, you
24 can't. So, you need to clarify that with the sponsor.

25 DR. SIMMONS: Well, let me ask you this. Since

1 there is no data in humans on the size of the lesion, I
2 would suggest that your results may not be as good, because
3 you need more power. I mean maybe you are not making as big
4 a lesion as you think you are making in humans.

5 I mean your studies have been done in animals,
6 right, to look at the depth of the lesion, which doesn't
7 always translate, so is it possible you really don't have an
8 accurate dose response curve?

9 DR. WHARTON: First, how are you going to measure
10 lesion size in humans? That data is unobtainable.

11 DR. SIMMONS: I would have thought that you had--
12 you know, 30 percent of the patients died, I mean there
13 should have been some autopsy data, right?

14 DR. WHARTON: There is no comparison to standard
15 lesions, so how are you going to get a comparison to a
16 standard RF? Plus, this is not a trial of standard versus
17 chilled ablation. It was compared to medical therapy, but
18 anyway you are not going to get that data easily by any
19 technology that I know. Maybe you could use MRI or
20 something like that, but that is not proven to be a good way
21 of lesion sizing. Comparing lesion sizes in humans can be a
22 very difficult issue.

23 So, short of some sort of way to measure lesions
24 in humans, you are going to be stuck with animal data. I
25 think if you look at the animal data that we can provide

1 you, or other studies, for that matter, that are published
2 in the literature, you will see that there is a pretty
3 consistent finding that the chilled ablation approach
4 results in larger lesion volumes, in most cases lesion depth
5 and width as well, in part because of the increased duration
6 that you are allowed to apply energy at higher powers. You
7 clearly limit the frequency of impedance rises.

8 DR. SIMMONS: But, you see, I would have thought--
9 you are saying that is a good thing--and I would have
10 thought that would have translated into something better.

11 DR. WHARTON: But how do you know it didn't?

12 DR. SIMMONS: Well, I mean your statistics show
13 that you are just as good as regular old RF. The fact is
14 there are many articles using just regular RF, not cooled
15 RF, that have better results.

16 DR. WHARTON: I would argue those are not
17 controlled trials, though.

18 DR. SIMMONS: I would argue this isn't a
19 controlled trial.

20 DR. WHARTON: I would argue it was, but anyway, we
21 could argue this back and forth.

22 DR. CALKINS: Actually, I think a simple way to
23 think about this is--I am actually very impressed that if
24 you are doing VT ablation with the standard catheter,
25 oftentimes you can't deliver much power. At 10 watts, 5

1 watts, if you have a very stable catheter position, that is
2 all the power you can give before you start heating.

3 In this catheter, the striking thing is you are
4 able to deliver more power, it routinely will give 30, 40
5 watts without any coagulum, without any impedance rise, so
6 to the degree that you are using an identical tip to what
7 standard catheters use, you are using an identical patch in
8 the back, you are giving more power, you know, the power is
9 going somewhere, you are making bigger lesions, so it really
10 allows you to give more power.

11 I was actually--I have looked at some of the data
12 Marcus came up with, was impressed, and, in fact, the
13 lesions were bigger although I hadn't looked at the little
14 40-degree lip, but the 30 and 50, certainly it is headed in
15 the direction you would expect.

16 DR. SIMMONS: It certainly would have been nice to
17 see an improvement in the statistics over the regular
18 radiofrequency catheter.

19 DR. ECHT: Remember, we were asked not to do a
20 comparison with regular catheters because that is off-label
21 use.

22 DR. SIMMONS: But you could have done a comparison
23 with your own catheter cooled versus not cooled.

24 Would you agree that based upon the fact that you
25 aren't clear about how deep these lesions are in humans,

1 that this catheter is not going to be indicated for right-
2 sided lesions until something is done? I mean for RV
3 lesions or for RV outflow tract lesions or atrial lesions.
4 I mean since you don't know depth and width.

5 DR. ECHT: This has been used in the patients with
6 non-ischemic cardiomyopathy. It has been used in the study,
7 not in huge numbers of patients.

8 DR. SIMMONS: How many? You are talking about RV
9 lesions, lung, septum?

10 DR. ECHT: We have recommended that lower powers
11 be used in those patients.

12 DR. SIMMONS: I think I am going to pass and let's
13 start on the second round of questions.

14 DR. TRACY: Let me see if I can come to some--
15 there is just some things that still trouble me a little
16 bit, but let me just kind of walk through this.

17 If you use those patients that actually receive
18 chilled tip ablation, the acute success rate is 63 percent
19 of those 61, and that is on page 6.3.2-6, so the acute
20 success is 63 percent.

21 Following these patients out--

22 DR. ECHT: No, that is not correct. That is the
23 long-term success in those with acute successes. It was 70
24 percent.

25 DR. TRACY: The last sentence there acute efficacy

1 using intention-to-treat analysis was 75 percent if having
2 no mappable VT to ablate was considered a success, and 63
3 percent if considered a failure.

4 So, to have no mappable VT that was ever
5 approached, I would take those out and say of those that
6 were mappable and treated, the acute success rate is 63
7 percent, because if you didn't ablate it, then, you cannot
8 count that as a success, so I think 63 percent is a more
9 accurate reflection of acute success.

10 So, you follow those people for a period of time,
11 and somewhere out there, at some point, many of them have
12 recurrent VT, on the order of 40 to 50 percent, something
13 like that, I don't have the specific numbers right here,
14 have some recurrent VT, presumably not the clinical VT, but
15 subjectively from the patient's experience, recurrent VT.

16 And you then take them and restudy them at two to
17 three months for inducibility, and again, the ablation
18 group, 69 percent have--of those that were restudied at two
19 to three months--69 percent are inducible to any VT, much
20 lesser inducible to the clinical VT as compared to the
21 controls, but nonetheless, 69 percent still have VT, and you
22 have the control group who received medication, and for
23 whatever reason, in some of that patient population,
24 medication had to be stopped or wasn't used, and so some
25 drug-free patients had ablation.

1 DR. ECHT: At two to three months, 93 percent of
2 the controls were on drugs, yes.

3 DR. TRACY: Fine, so that you are studying on-drug
4 patients who still have the same inducibility rate as
5 ablation patients, but that is not the issue.

6 At some point, those patients, a bunch of those
7 patients ended up getting ablated, which already maybe some
8 of the ablation patients had had recurrent VT at that point
9 also, and didn't have anywhere else to go, they had already
10 had their ablation.

11 So, from the patient subjective standpoint, there
12 is a lot of shocks going on here, whether they have had
13 ablation or whether they have had drug therapy, there is a
14 lot of defibrillation therapies being delivered.

15 I don't think anybody could disagree with that.

16 DR. ECHT: We have the number of VT episodes in
17 the two months prior and the two months after in all these
18 patients, in the patient groups except for the controls,
19 because since the controls could cross over after one, we
20 can't look at VT density post-randomization in them.

21 Actually, if you look at VT inducibility at two to
22 three months on Table 11, that the induction of clinical VT
23 was almost statistically different in the controls and the
24 ablation groups, where in the ablation groups, 16 percent
25 had clinical VT inducible at three months, in the controls

1 it was 46 percent.

2 So, yes, there was overall inducibility of 69
3 percent in each, but, you know, in terms of targeted
4 arrhythmias, it was substantially different.

5 DR. TRACY: I would agree with that. What I am
6 trying to figure out, we agree that probably you are not
7 providing mortality benefit. You are not getting rid of
8 inducible VT. What is it that you are doing?

9 DR. ECHT: I sympathize with you. Frankly, when I
10 sort of joined the company, had the same problem with the
11 endpoint being--I understand and I know that our
12 investigators could speak to the fact that even though the
13 published literature looked at recurrence of target VT, that
14 when you are looking at recurrence from an ICD intracardiac
15 electrogram, and saying that was or wasn't a targeted VT,
16 there is a lot of guessing going on, and that this is a more
17 correct endpoint.

18 On the other hand, it is a very nonspecific
19 endpoint, and it occurred to me that what we are really
20 doing for these patients who had really problem VT, very
21 high density VT, was that we are taking their problem VT,
22 the VT that was causing them most of their symptoms, and
23 getting rid of that.

24 A lot of them already had defibrillators, so they
25 are hemodynamically unstable VTs, that they get shocked from

1 once or twice a year, they will still have, but they won't
2 be getting 20 shocks a month.

3 It seemed to me that one way of looking at this
4 would be to look at the VT density. We did capture the
5 number of VT episodes in the two months prior, and we also
6 were capturing the VT episodes at each follow-up visit, so
7 we were able to do this.

8 Now, this was not an endpoint for the study, and
9 therefore, we are not supposed to show this as a sort of
10 part of an endpoint of our study, but it is ancillary data
11 that was provided in your PMA, so I am allowed to show it to
12 you now.

13 It also is a way of comparing the results here
14 with a published study that is also provided in your packet
15 by Strickberger, where they looked at VT density. They
16 didn't look at the two months before and after, they looked
17 at the VT density per month before versus afterward, and our
18 data compares very well, and I can just show that.

19 DR. STUHMULLER: Can I clarify a procedural
20 point? So, this is data that is in your PMA, is that
21 correct?

22 DR. ECHT: This is data that is in the PMA.

23 DR. STUHMULLER: Is this a new analysis of data
24 that is not included in the panel pack?

25 DR. ECHT: No.

1 DR. STUHMULLER: This is an analysis that is in
2 the panel pack?

3 DR. ECHT: This table comes from the panel pack.

4 DR. STUHMULLER: Okay. That is what I needed to
5 clarify.

6 [Slide.]

7 DR. ECHT: If you sort of pool these subcohorts,
8 the number of VT episodes in the two months before support
9 these three pooled groups was a mean of 25 episodes of VT,
10 and afterward it was reduced to 7 overall, and our
11 investigators got together and thought, completely
12 arbitrarily, but came up with the idea that if the patients
13 had at least a 75 percent greater reduction in the number of
14 VT episodes after compared to before, they would consider
15 that a reasonable clinical outcome for these particular
16 groups of patients. Using that definition, 73 percent of
17 patients had at least a 75 percent reduction.

18 [Slide.]

19 The other analysis I have is if you split out
20 those patients who had acutely successful ablation
21 procedures versus acute failures, you will find--and that
22 shows up on Table 28--that the reduction in VT episodes
23 after ablation was very significant in those patients in
24 whom the acute ablation was considered a success versus
25 those that it was considered a failure in which there was

1 not a significant reduction.

2 It is another way to look at it. I don't know if
3 the investigators want to comment at all about their
4 experiences.

5 DR. TRACY: Actually, I think this is really the
6 most compelling information that you have in the whole
7 thing, because you don't make people live longer, you don't
8 get rid of all the attacks. The control group is not really
9 a good control group because--it's just not.

10 But this is probably the most compelling
11 information I think in the whole thing. I really think it
12 is the most important piece of the whole picture, but it
13 does argue a little bit against--getting back to our safety
14 and effectiveness labeling at some point--we still see here
15 3.4 plus or minus 8.7 VT episodes, so these are still people
16 who have VT, these are people who need a net, a
17 defibrillator net.

18 DR. ECHT: What I don't have is what subgroup of
19 that population had none, and that would potentially be
20 helpful.

21 DR. SIMMONS: We will start over here with Dr.
22 Aziz.

23 DR. AZIZ: Just a little technical question. If
24 patients were on heparin, you mentioned that is a
25 contraindication, would you consider using low molecular

1 weight heparin in those cases?

2 DR. ECHT: In this trial, if they had a
3 contraindication to heparin, they couldn't be in the trial,
4 so I really can't comment about alternative medications. I
5 would wonder what clinically the investigators have done as
6 regards patients who have contraindications of heparin, but
7 needed an RF ablation, a standard RF ablation.

8 DR. AZIZ: The question is I think the low
9 molecular weight heparin would be if someone had a
10 contraindication to coumadin, and they had, let's say, a
11 thrombus, and you want to anticoagulate them for three weeks
12 before the procedure, that would be a logical alternative
13 strategy.

14 Usually, if they have a contraindication to
15 heparin, it is because they have an aneurysm in their brain
16 or whatever, or have had a stroke and they maybe bleed, that
17 kind of thing, where you would expect low molecular weight
18 heparin had the same problem as standard heparin. In those
19 patients I think you did a procedure if they needed it done
20 without anticoagulation, but you would have to make sure the
21 patient was aware of the risks associated with that.

22 DR. AZIZ: Or if you had heparin-induced--

23 DR. CALKINS: Thrombocytopenia, I am not sure, I
24 guess that is not a problem, low molecular weight heparin.

25 DR. BRINKER: The cross-reactivity is very high

1 between low molecular weight heparin. You would have to
2 think, there are other drugs that don't cross-react that you
3 could use acutely, but if it is heparin-induced
4 thrombocytopenia, if you give it just very short term just
5 to cover the procedure, there is no problem if that is your
6 concern.

7 DR. SIMMONS: Go ahead, Dr. Brinker, second round.

8 DR. BRINKER: I came here wondering what the role
9 of this form of therapy is more than what this device
10 specifically is, and I am going to leave here with the idea
11 that this form of therapy is like a very effective
12 antiarrhythmic drug. It is not totally effective, but it is
13 effective, and it may reduce the incidence of symptomatic or
14 defibrillator-triggered ventricular tachycardia, which I
15 would assume is beneficial for the patient at least in terms
16 of his quality of life.

17 I don't think there is any claims beyond that, and
18 I am pretty much happy with the rest of the study. I
19 wouldn't say that a 2 percent mortality is a low risk
20 procedure when it is four times the mortality of angioplasty
21 right now, but I understand the tradeoffs in terms of
22 quality of life in these patients, and it is certainly
23 acceptable.

24 DR. SIMMONS: Dr. Vetrovec.

25 DR. VETROVEC: Just to follow up on what you just

1 showed, let me make sure I understand what you just said.
2 You don't know the number of patients who had no VT after
3 this procedure and follow-up?

4 DR. ECHT: We could get you that. We have that
5 data. I haven't analyzed in that exact way, but it could be
6 done, you know, in an hour.

7 DR. VETROVEC: I don't have anything else.

8 DR. SIMMONS: Dr. Crittenden.

9 DR. CRITTENDEN: I don't have any other questions.

10 DR. WILBER: If I could just respond to the
11 previous question. In our own data, the number of patients
12 who have had absolutely no recurrences is 40 percent.

13 DR. ECHT: Do you think about half of your series
14 were in this cooled ablation study, is that about right?

15 DR. WILBER: Yes.

16 DR. ECHT: So, approximately 30 of those patients
17 were included in this study.

18 DR. SIMMONS: I really don't have any other
19 questions. Mr. Jarvis, do you have any questions?

20 MR. JARVIS: I have no questions.

21 DR. SIMMONS: Does anyone have any questions for
22 the FDA before we close it for discussion? Any questions
23 for the FDA?

24 Okay. I guess we will close it to the company,
25 step back, and I think it is time for open panel discussion

1 here, if somebody wants to start.

2 **Panel Discussion**

3 DR. TRACY: I am going to just jump in because I
4 would just like to reiterate that I would have felt better
5 if there was a comparison, if this study had been set up at
6 some point to compare a standard RF catheter versus a chill
7 tip. I understand that that was not possible, it was not
8 asked, and we don't have that.

9 We don't have human data, but we do have animal
10 data. The lesions that are being created are bigger, and
11 bigger is not always necessarily better, however, we have
12 described here something that doesn't make people live
13 longer, it doesn't get rid of all VT. In some people it
14 may, but as an overall population, it does not, but it
15 probably does make people feel--it does make people feel
16 better compared to drugs or nothing.

17 Compared to standard ablation, we don't know. The
18 price that we pay is the acute complication rate that we
19 have here in this study, and this is by no means a low risk
20 procedure as has been pointed out, but again, compared to
21 having 25, 40 episodes of VT a month, it is a price that
22 many people I think in that circumstance would be willing to
23 pay.

24 I think that summarizes what I get out of this.

25 DR. SIMMONS: I guess part of my frustration as an

1 electrophysiologist is I was hoping a whole lot more from
2 this. I mean I was really hoping that--I guess I wanted the
3 cooled idea to work, you know, I wanted the cooled ablation
4 idea to have some merit, and I am walking away from here not
5 convinced that this has been proven at all, that this is an
6 ablation catheter that can be used for VT just like any
7 other ablation catheter, but I remain unconvinced that the
8 cooled portion of it has been shown to be of any value, and
9 that is a shame, because I understand that it couldn't have
10 been compared against a standard catheter, but it could have
11 been compared against itself, and that would have even given
12 the investigators even more enthusiasm maybe to do the
13 study, which is generally the guiding rule about how many
14 patients get enrolled in the study.

15 So, I don't see it as being worse than off-label
16 use of the other ablation catheters. I am just disappointed
17 that the cooled portion of it didn't really show a dramatic
18 increase in success.

19 An overall complication rate, you know, in spite
20 of some of the things that have been said, the complication
21 rate in here is just a little bit higher than many of the
22 articles including some that one of the investigators here
23 has published, with 1 out of 21 complications in a patient
24 with a VT study.

25 So, it is a little bit higher than normal, but

1 again this is a sicker population and it is a small sample
2 size, and those things may even out. I don't think it is so
3 dramatic to warrant rejection.

4 Does anyone else have any comment?

5 DR. STUHLMULLER: I would just like to reiterate
6 again the issue today is, is this device safe and effective
7 relative to its proposed indication for use, and not the
8 off-label use of other devices. So, I would just like to
9 ask the panel again to stay focused on that topic, is this
10 device safe and effective in relation to its proposed
11 indications for use.

12 DR. SIMMONS: But don't you have to compare that
13 to what is standard being done, and also those things have
14 been in the panel packet. I mean all those articles using
15 RF catheters for VT ablation are in the panel packet, so
16 don't we have to at least acknowledge that that is something
17 that is being done?

18 DR. CALLAHAN: Well, yes, you can certainly
19 acknowledge the fact, I mean it is cooled, so you can
20 certainly address whether you think the cooling has done
21 anything. In the end, there is still a claim which doesn't
22 seem to depend on it being cooled or not.

23 DR. SIMMONS: Does anyone else have any comments?

24 DR. TRACY: Just to stick with the safety and
25 effectiveness and how this thing is intended to be used, I